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Pubblicazioni

- The role of quality of life tools in superficial venous disease.
S. Zappadu, S. Onida, A.H. Davies, T.R.A. Lane n. Section of Vascular Surgery, Department of Surgery and Cancer, Imperial College London, Charing Cross Hospital, Fulham Palace Road, W6 8RF London, United Kingdom. 21/04/2016
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Sara Zappadu, Elisabetta Tanda, Giulia Pistincu, Gabriele DeDonno, Genadi Genadiev, Giuseppe Deiana, Mario Moro, Francesco Spanu, Stefano Camparini

- Refractory Chylothorax Secondary to Sizeable Azygos Vein Hemangioma: Tailored Multimodal Treatment of a Challenging Case Report 31/12/2022

Paolo Albino Ferrari, Federico Fusaro, Antonio Ferrari, Alessandro Tamburrini, Giulia Grimaldi, Massimiliano Santoru, **Sara Zappadu**, Elisabetta Tanda, Sonia Nemolato, Simone Comelli and Roberto Cherchi

Abstract

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 - o Poster: EVAR + IBE e reverse candy plug technique per l'esclusione del falso lume in aneurisma aortico addominale post- dissecazione aortica cronica
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 - XVIII Congresso Nazionale SICVE Firenze, 21-23 Ottobre 2019
 - Patologia Vascolare degli arti inferiori: arteriopatia e piede diabetico, malattia venosa cronica, Cagliari 18-19 Settembre 2020
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Curriculum vitae

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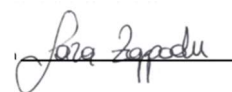
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Review

The role of quality of life tools in superficial venous disease

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ABSTRACT

Superficial venous disease (SVD) is a common condition in the Western world, with recognized, negative effects on mood and quality of life (QoL) in those affected. Numerous tools exist to assess QoL in patients with SVD. The aim of this article is to review the literature on the role of QoL assessment tools in this disease group, describing the most commonly used instruments and their relevance, assessing the relationship between clinical and functional assessment tools, delineating the correlation among physician and patient reports and discussing the importance of translation.

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Contents

1. Introduction	18
1.1. Epidemiology	18
1.2. Classification systems for SVD	18
1.2.1. Clinical assessment systems (CEAP)	18
1.3. The importance of quality of life	18
1.4. QoL instruments	19
1.5. Generic QoL instruments	19
1.5.1. The Nottingham Health profile	19
1.5.2. Short form 36	19
1.5.3. Short form 12	19
1.5.4. Short form 8	19
1.5.5. The EuroQol-5D	19
1.5.6. Symptom Rating Test (SRT)	19
1.6. Disease-specific instruments	19
1.6.1. The Aberdeen Varicose Vein Questionnaire (AVVQ)	19
1.6.2. The Chronic Lower Limb Venous Insufficiency (CIVIQ)	20
1.6.3. VEINES-QoL/Sym Questionnaire	20
1.6.4. Specific Quality-of-life and Outcome Response-Venous SQOR-V	20
1.6.5. Charing Cross Venous Ulcer Questionnaire (CXVUQ)	20
1.6.6. VVSymQ	20
1.7. Correlation between QoL and clinical, duplex, anatomical and hemodynamic assessment	20
1.8. Physician reported vs Patient reported outcomes	21
1.9. Linguistic translation of QoL measures	21

Abbreviations: CVD, Chronic venous disease; SVD, Superficial venous disease; CEAP, Clinical Etiological Anatomical Pathophysiological; QoL, Quality of Life; HRQoL, Health related quality of life; NHP, Nottingham Health Profile; SF-36, Short Form 36; SF-12, Short Form 12; SF-8, Short Form 8; VAS, Visual Analogue Scale; PROMs, Patient Reported Outcome Measures; QALY, Quality Adjusted Life Years; SRT, Symptom Rating Test; AVVQ, Aberdeen Varicose Vein Questionnaire; CIVIQ, Chronic Venous Insufficiency Questionnaire; SQOR-V, Specific Quality of life and Outcome Response-Venous; CXVUQ, Charing Cross Venous Ulcer Questionnaire.

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2. Conclusion	21
Submission declaration	21
References	21

1. Introduction

Chronic venous disease (CVD) can be defined as “(any) morphological and functional abnormality of the venous system of long duration manifest either by symptoms and/or signs indicating the need for investigation and/or care”. This describes both visual and functional manifestations of a poorly functioning venous system; both the superficial and/or deep venous networks may be affected. The signs and symptoms of CVD can significantly impact on the quality of life of those affected due to their chronicity.

1.1. Epidemiology

Patients with superficial venous disease (SVD) can present with a number of symptoms, including heaviness, itching, aching and throbbing in the lower limbs; often these are worsened by prolonged standing. Amongst of the most common presentations of chronic venous disease are varicose veins, tortuous, elongated superficial veins (> 3 mm in diameter) usually found in the lower limb. Varicose veins represent one of the most prevalent conditions in the Western world. Previous epidemiological studies have found that the prevalence of SVD has a relationship to gender, age and parity, and that the reported epidemiology is very heterogeneous. Up to 80% of the population is affected by telangiectasiae (also known as spider or thread veins), while varicose veins affect 20–64% of the population [1]. A gender difference has been reported, with 1–73% of women and 2–56% of men affected respectively [2]; further studies have however found the prevalence to be similar in men and women [3,4]. A lower proportion of the population (5%) is affected by more advanced stages of venous disease (including skin staining and scarring) with a prevalence of healed and active venous ulcers estimated at 1–2% [5].

1.2. Classification systems for SVD

The assessment of SVD can be defined as clinical or functional; similarly, it can be disease-specific or general.

1.2.1. Clinical assessment systems (CEAP)

The Clinical Etiological Anatomical Pathophysiological (CEAP) classification (Table 1) was developed as an international, standardized system used to describe the clinical objective presentation of CVD [6]. It is the most widely used classification system, exploring clinical, anatomical and duplex characteristics, and enables comparisons between different reports in the literature due to its standardized nature.

Despite its international endorsements, CEAP is far from being a highly comprehensive or reliable assessment system [7,8]. CEAP is a purely descriptive classification and is not easily translated into a quantifiable scoring system. For example this classification does not include mixed arterial and venous disease, venous neuropathy and venous claudication [9]. Furthermore, CEAP does not provide any information regarding disease severity or patient perception of disease status. It is a static measure of disease that does not reflect clinical improvement following intervention; for example, a patient who has previously suffered with venous ulceration that has healed will always be classed as a C5 patient. CEAP is a good initial classification system for patients with chronic venous disease; however it is not a measure of disease

severity and should be used in conjunction with alternative assessment systems, such as the venous clinical severity score (VCSS).

VCSS was developed to supplement the CEAP classification [10]. It offers a broad quantification of disease severity and is not a detailed descriptive tool for CVD in an individual patient. VCSS takes into account the degree to which patients are affected by CVD, the progression of symptoms and gives additional weight to more severe clinical stages of disease. It has been reported as suitable for measuring changes after surgery, but in studies investigating the use of compression stockings it may not be appropriate [11]. VCSS is responsive to changes in disease severity over time and in response to treatment but again, is a purely clinical measure.

Clinical assessment systems do not necessarily reflect patients' perception of quality of life (QoL). Specific instruments that take this into account are very useful in the assessment of patients with SVD, and can help clinicians to better understand the global, holistic impact this condition has on those affected.

1.3. The importance of quality of life

The World Health Organization defines quality of life as a state of complete physical, mental, and social well being, and not merely the absence of disease. In fact, disease states have multiple dimensions, including clinical presentations, results of investigations and functional effects. However, patient perception of disease and the impact of illness on daily life are of extreme importance when estimating disease burden. QoL assessment tools aim to quantify this dimension into scoring systems that may be of use in terms of determining disease severity and response to treatment [7,8,12–14].

Table 1
CEAP Classification.

C: Clinical classification
C0: no visible or palpable signs of venous disease
C1: telangiectasia or reticular veins
C2: varicose veins
C3: oedema
C4a: pigmentation or eczema
C4b: lipodermatosclerosis or atrophie blanche
C5: healed venous ulcer
C6: active venous ulcer
S: symptomatic, including ache, pain, tightness, skin irritation, heaviness, muscle cramps
A: asymptomatic
E: Aetiological classification
Ec: congenital
Ep: primary
Es: secondary (eg post thrombotic)
En: no venous cause identified
A: Anatomical classification
As: superficial veins
Ap: perforator veins
Ad: deep veins
An: no venous location identified
P: Pathophysiological classification
Pr: reflux
Po: obstruction
Pr.o: reflux and obstruction
Pn: no venous pathophysiology identifiable

Table 2
Quality of life assessment tools.

Clinical Classification	Health related generic tools	Disease specific tools
CEAP	SF-36	AVVQ
VCSS	EuroQoL, 5D	CIVIQ-20
VSDS	NHP	SQoR-V
VDS		VEINES-QoL/Sym
		VVSymQ
		CXVUQ

Quality of life evaluation is particularly important in CVD. Patients often complain of pain, aching and a limitation in their daily activities, particularly for those who have occupations that lead them to stand for a long time.

Importantly, the different dimensions of disease do not always correlate. Clinical (or physician) assessment may be quite different to subjective patient experience. Similarly, the functional impact on the patient may also be very different. A comprehensive assessment should include all factors. The ideal QoL tool must be sensitive over time and after treatment, representative of disease severity, reproducible in different populations and able to detect disease progression.

1.4. QoL instruments

Quality of life instruments can be generic or disease-specific (Table 2). Generic tools have been developed to compare patient populations with different diseases; specific tools have been developed to understand the quality of life dimension in those affected by a specific disease. Using both QoL modalities is advisable to get a holistic view of patient status [15].

1.5. Generic QoL instruments

1.5.1. The Nottingham Health profile

The Nottingham Health profile is a generic QoL instrument has been employed in several clinical areas such as cardiovascular disease, rheumatological disease, and in patients with leg ulceration [16]. It is divided in 38 questions converging on six areas of daily life: energy, pain, emotional reaction, sleep, social isolation and physical mobility. Franks and Moffat reported the use of NHP on a sample of patients with chronic venous ulceration. NHP was used to interview the patients before and after treatment with compression bandaging. It was found to be improved in patients whose ulcer had healed compared to those where the ulcer failed to heal, indicating sensitivity to change in ulcer status [17].

1.5.2. Short form 36

One of the most widely employed generic instruments to measure quality of life is the Short form 36 (SF-36), which has been shown to have extensive applications in several disease conditions and extensive validation in several populations [16]. It consists of 36 items over 8 dimensions covering physical and psychological well being: physical functioning, physical disability, bodily pain, general health perception, energy/vitality, social functioning, role limitation due to emotional problems and mental health. The SF-36 questionnaire has been employed as a general measure of health related quality of life (HRQoL) in patients with venous ulcers [18]. However, this questionnaire should be accompanied by a disease-specific instrument to assess the effect of therapy in the venous ulcer population. To utilise SF-36 scores in cost-effectiveness analysis requires conversion via utilities.

1.5.3. Short form 12

The SF-12 employs 12 questions and can be completed in two

to three minutes. It was developed to be a short, practical, and valid alternative to the SF-36. In fact, it covers the same aforementioned 8 health domains, with one or two questions relevant to each section. SF-12 has been employed in patients with venous disease; Shepherd et al. [19] utilised it in conjunction with the AVVQ to assess quality of life prior to varicose vein intervention, while Darvall et al. [14] employed it to determine the relationship between lower limb symptoms and generic quality of life in patients with varicose veins. Studies have shown that the SF-12 closely mirrors results from the 36-item short form [20] and, due to its quick completion, may therefore be the instrument of choice for a brief generic assessment of quality of life [21].

1.5.4. Short form 8

The SF-8 also provides a measure of generic physical and mental status with eight questions covering the eight SF-36 domains. It presents a strong correlation with SF-36 and is more brief than the SF-12, thus easier to complete and translate. However, it is, predictably, less precise than the SF-36 [22].

1.5.5. The EuroQoL-5D

The EuroQoL-5D consists of five dimensions (mobility, self care, usual activities, pain/discomfort, anxiety/depression), each divided in three levels (no problems/ some problems/ unable to do – 3 L) or five levels (no problems/slight problems/ moderate problems/ severe problems/ unable to do – 5 L). The visual analogue scale (EQ-VAS) allows patients to subjectively estimate how good or bad their general health state is on a scale from 1 to 100. The EuroQoL 5D is a simple measure applicable to a wide range of health conditions and treatments [23]. Importantly, it is currently part of the Patient Reported Outcome Measures (PROMs) questionnaires for venous disease intervention, as it is the preferred instrument for the estimation of Quality Adjusted Life Years (QALYs) [24,25].

1.5.6. Symptom Rating Test (SRT)

The Symptom Rating Scale is considered an important questionnaire to understand the quality of life of patients with SVD, and it takes into account the importance of patients' psychological status, including the presence of depression and anxiety [16]. It has been employed as a quality of life instrument in patients with leg ulceration.

1.6. Disease-specific instruments

Disease-specific instruments have been developed to reflect patients' views of their health specific to a particular condition. Three important disease-specific QoL measures can be employed in patients with chronic venous disease: the Aberdeen Varicose Vein Questionnaire (AVVQ), the Chronic Venous Insufficiency Questionnaire (CIVIQ) and the VEINES-QoL/Sym.

1.6.1. The Aberdeen Varicose Vein Questionnaire (AVVQ)

The AVVQ, developed in 1993, has been used to determine the quality of life of patients affected by varicose veins before and after treatment. It consists of 13 questions relating to numerous aspects of venous disease, and allows patients to express a subjective measure of the extent of their varicosities by enabling them to draw a diagrammatic representation of their veins. Also known as manikin diagram (question 1), this is followed by 12 questions exploring a number of domains, including the experience of pain, leg swelling, interference with social or domestic activities and the cosmetic implications of the presence of varicose veins [26]. The AVVQ can be applied to investigate the bio psychosocial attributes of patients with varicose veins, including the effect on daily functions of specific signs and symptoms. It has been described as a useful disease-specific tool in assessing functional outcome after

treatment for chronic venous disease and is currently being used in conjunction with the EQ-5D as the disease-specific QoL measure in the PROMs questionnaires [24,27].

Recently, a structural change to the AVVQ has been proposed, relating to question 1. This can be a time consuming question that is often not completed by patients. Staniszewska et al. [13] correlated AVVQ scores obtained with and without the manikin diagram in 32 patients. The authors demonstrated a good level of agreement between the two groups, raising the question of whether the manikin diagram could be entirely removed from the questionnaire, potentially resulting in a more time and cost-effective AVVQ.

1.6.2. The Chronic Lower Limb Venous Insufficiency (CIVIQ)

CIVIQ-20 measures individual symptoms (ankle or leg pain severity) and the influence of leg problems on usual activities, physical role, social role, sleep and emotional functions. It is a sensitive instrument to monitor the key dimensions of quality of life impaired by SVD and to assess changes with treatment. It consists of 20 questions covering four QoL domains: pain (four items), physical (four items), social (three items), psychological (nine items). Despite its sensitivity, CIVIQ 20 was found to lack stability in the social dimension, particularly with respect to questions directly related to cultural norms or differences, which cannot be translated reliably in different languages [28].

The CIVIQ-14 was therefore developed with the aim of being a more stable and psychometrically validated questionnaire derived from CIVIQ-20. Six 'unstable' items were eliminated and the social and physical dimensions were combined, resulting in 14 items divided in three dimensions (pain, physical and psychological). Psychometric assessment demonstrated that CIVIQ-14 was a reliable, valid and sensitive instrument, applicable to international studies of patients with chronic venous disease [29].

The AVVQ and CIVIQ are two validated questionnaires demonstrating significant correlation; it is, however, important to highlight that these questionnaires are significantly different: AVVQ gives more importance to the physical aspects of disease, while CIVIQ provides a more global assessment. Furthermore, the AVVQ is validated for use in patients with varicose veins and venous ulceration.

1.6.3. VEINES-QoL/Sym Questionnaire

This questionnaire has been employed in both superficial and deep venous disease and is used to assess a broad range of signs and symptoms associated with chronic venous disease [30]. Because of its general nature, the VEINES-QoL/Sym may not be sufficiently sensitive to measure changes in symptomatology in patients with varicose veins [12]. Its advantages include the fact that it is brief, well validated and covers important general domains relevant to CVD, such as limitations in daily activities, psychological factors and items regarding changes in the past year [16]. VEINES-QoL/Sym has also been successfully employed to measure QoL in patients with deep venous thrombosis and post-thrombotic syndrome.

1.6.4. Specific Quality-of-life and Outcome Response-Venous SQOR-V

This is a disease-specific questionnaire consisting of 46 multiple-choice questions divided into 5 domains including physical discomfort, appearance, restriction in movements, risk, and threat to health and emotional problems. It is based on patient reported symptoms and does not include clinical signs [8]. A study by Shepherd et al. [8] demonstrated a strong correlation between the SQOR-V and the AVVQ in patients with chronic venous disease; however, it is important to note that the AVVQ attributes more weight to the presence of skin changes, ulceration and varicose veins [8,27]. Conversely, the SQOR-V is not based on clinical signs

but only on symptoms, and was specifically developed to allow for a more sensitive evaluation of the functional impact of venous disease in patients with CEAP classes C1-C3 [8].

1.6.5. Charing Cross Venous Ulcer Questionnaire (CXVUQ)

The CXVUQ is quality of life instrument specifically designed for patients with venous leg ulcers [18]. It was developed for use in conjunction with SF-36 to be employed in the pre and post-intervention assessment of individuals with ulceration, and has been described as a valid and reliable questionnaire with discriminant characteristics, despite queries regarding its scoring [31].

1.6.6. VVSymQ

VVSymQ is a new questionnaire uniquely focused on key symptoms of varicose veins, making it a useful adjunct in the assessment of patient experience pre and post-intervention for SVD. VVSymQ has been employed in clinical trials to assess the efficacy of varicose vein treatment in patients with superficial venous insufficiency. The questionnaire was developed in accordance with the United States Food and Drug Administration (US FDA) Guidance for Patient Reported Outcomes (PROs) [12]. It assesses symptom change over days or in a short time frame, unlike the AVVQ (which enquires about symptoms over a span of two weeks) or the VEINES-QoL/Sym/CIVIQ-20 (over four weeks) [12]. The VVSymQ has been described as a reliable, valid instrument uniquely focused on varicose veins symptoms pre and post intervention.

The presence of so many quality of life assessment tools can make the choice of the "optimal questionnaire" challenging. It is clear that certain disease-specific questionnaires have been developed with particular patient groups in mind (e.g. varicose vein vs ulcer patients). Furthermore, depending on the research question to address, different disease-specific and general tools can be employed. Is one assessing the clinical response to treatment? Psychological effects? Health economic evaluation? All these factors must be kept in mind when making a choice regarding the questionnaire to employ. Regardless, several studies have demonstrated that employing both disease specific and generic tools gives a global assessment on the impact of disease on patients' quality of life, and this should be encouraged [16]. Questionnaire fatigue is a significant problem in clinical studies and therefore a balanced, but thorough set is desired [32,33].

1.7. Correlation between QoL and clinical, duplex, anatomical and hemodynamic assessment

A global assessment of SVD includes clinical examination, investigation of the anatomical and hemodynamic status (duplex ultrasound) and a quality of life assessment. Duplex ultrasound is a safe, non invasive imaging modality that has been described as the gold standard investigation for SVD [34]. Importantly, if duplex ultrasound and clinical assessment are measures used to quantify disease severity, quality of life measures should, theoretically, correlate with them.

There is evidence that correlations do exist, however, these are difficult to interpret. Shepherd et al. assessed the correlations between venous disease specific-QoL measurements (AVVQ and SQOR-V, SF-12), hemodynamic (duplex ultrasound and digital photoplethysmography), anatomical and clinical outcomes (VCSS, CEAP) in patients undergoing treatment for varicose veins at baseline and at 6 weeks post treatment [8]. The authors found that following intervention, whilst there was an improvement for each outcome measure, the correlations between these improvements were weak [8]. Quality of life questionnaires showed a strong correlation between them, particularly the AVVQ and SQOR-V. Increasing CEAP class corresponded to a deterioration in quality of

life in the AVVQ score, although this was not reflected in the SQOR-V score, which revealed a worsening QoL score for patients with C3 disease compared to C4 disease. This may be reflective of the sensitivity of the SQORV in evaluating the functional impact of venous disease in patients with CEAP class C1–C3. It is also interesting that there was no correlation between quality of life questionnaires and digital photoplethysmography: venous refill time in patients with unilateral disease did not correlate with either the AVVQ, nor the SQORV before and after treatment. Furthermore, weak correlations were found between AVVQ and anatomic reflux. From these findings, one can deduce that the presence of anatomical reflux does not necessarily correlate with functional impairment or clinical disease, and it is therefore important to include disease-specific questionnaires in the assessment of the patient with SVD. This concurs with the practical clinical observation that not all reflux is symptomatic.

Gibson et al. reported similar findings [35]; they investigated the relationship between patient quality of life measures (CIVIQ-20 and VEINES (QoL/Sym) and GSV diameters in patients with GSV incompetence. The results showed a poor correlation between vein diameter and QoL, suggesting that duplex cannot be used as a unique assessment criterion in these patients.

QoL is known to deteriorate with increasing CEAP grade, with physical impairment in C6 disease comparable to the disability seen in congestive cardiac failure and chronic lung disease [7]. Varicose vein intervention aims to reduce clinical symptoms and improve patient QoL. Treatment is not limited to complicated disease (e.g. bleeding, ulceration), but is advised for patients of any CEAP stage with symptoms of venous disease [36]. The importance of treatment in this patient group is demonstrated by the impact of depression in patients with symptomatic varicose veins. 1 in 10 adults in Britain suffers from depression at any one time, and depression is twice as common in patients with venous disease compared to the general population [37].

1.8. Physician reported vs Patient reported outcomes

Clinical (physician reported) and QoL (patient reported) outcomes enable evaluation of a single condition from two different perspectives. It has been shown that these assessment measures correlate in large studies.

Lonzano Sanchez et al. assessed 1560 patients with CVD, demonstrating a correlation between the severity of disease as objectively assessed by clinicians and the subjective patient perception of health. The clinical viewpoint was evaluated by CEAP and VCSS, while patient perception of QoL was determined by SF-12 and CIVIQ-20 [38]. The results revealed that increasing CEAP grade was directly proportional to worsening QoL in patients. Both questionnaires indicated that the QoL reduced significantly with increasing CEAP grade.

Kaplan et al. assessed a sample of 2404 patients employing two clinical criteria: visual inspection and duplex ultrasound scanning [39]. Patient reported QoL was then assessed using the SF-36. The authors found a high correlation between clinical assessment and the physical component of the SF-36, but, interestingly, not the mental health component.

1.9. Linguistic translation of QoL measures

QoL questionnaires must be translated to ensure validity when assessing patient cohorts from different countries. The AVVQ has been translated in Dutch and Portuguese [40,41], while the CIVIQ-20 has been translated and validated in 27-languages, and translated, without using internationally accepted translation methodology, in an additional 11 languages [42]. The translations were validated using forward/backward methodology in patients with

CVD and with CEAP grade C2–C4; patients with ulcers were excluded. The importance of reliability, validity and feasibility of the different translations is linked to the necessity for a common language between doctors from different countries. Populations from different countries may have distinct, culturally influenced perceptions of pain, sensibility and lifestyle; in light of this, each questionnaire should be adapted to its target population. During the translation of questionnaires in different languages, equivalent content, semantics and question technique must be verified.

In the translation of CIVIQ, the content of each question has cultural relevance. For instance, in countries where travelling by car is unusual and the population uses public transport, the question “how much difficulty did you have in travelling by car?” should be changed with “how much difficulty did you have in travelling by train or bus?” Similarly, the question “How much trouble have you experienced performing household tasks such as standing around the kitchen, carrying a child in arms, ironing, cleaning the floor, or DIY” has been adapted for Austria with the addition of gardening (in light of the fact many houses have gardens).

The semantics are most difficult to translate because specific words cannot be translated: “gêne” in French means trouble, whilst in Canadian French it translates as embarrassment [23]. “Piétiner” (stamping) is replaced with “standing and moving” in English. These examples highlight how important it is to adapt the questionnaire to different languages. CIVIQ was developed in France and subsequently translated; in both the original and international versions the five conditions required for validation were respected: relevance, acceptability, reliability, construct validity and sensitivity [23]. However, respecting these conditions and finding the correct equivalent term in each questionnaire item is a difficult challenge.

2. Conclusion

QoL has been shown to be of great importance in patients with venous disease. Both disease-specific and general questionnaires exist assessing different QoL dimensions. Clinical classification systems such as CEAP provide a one-dimensional assessment of patient status. This has been highlighted especially in chronic venous insufficiency and in uncomplicated varicose veins, where mortality is low but morbidity is high. QoL tools, in combination with clinical data, provide a global picture of a patient's condition and are of importance in the assessment of patients undergoing intervention, in the evaluation of the effect of intervention and in health economic analysis. This is demonstrated by the increasing use of quality of life data as a primary outcome measure in large clinical trials; the VANISH2 study [43] employed VVSymQ as a primary endpoint, while the CLASS trial [44] employed both disease specific and general quality of life outcomes.

Submission declaration

The authors declare that this work has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and that, if accepted, it will not be published elsewhere without the written consent of the copyright-holder.

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It is not appendicitis? An uncommon case of appendiceal tumour

A 52-year-old woman was admitted to our surgical department with a 1-month history of recurrent, periumbilical colicky pain, which intensified in the 24 h prior to hospital admission.

Associated symptoms were nausea and vomiting. She denied having any changes in bowel habits, weight loss, fever or blood in stool.

Her past medical history was significant for Hashimoto's thyroiditis, cervical cancer, β -thalassemia major and chronic venous insufficiency.

Physical examination revealed multiple café-au-lait spots on the skin, axillary and inguinal freckling and diffuse abdominal plexiform neurofibromas associated with skin disfigurement (Fig. 1a).

On initial examination, abdominal palpation revealed tenderness localized in mesogastrium and right lower quadrant, without muscular rigidity. Blood tests and serum levels of inflammatory and tumour markers were normal.

An abdominal ultrasound scan was carried out, showing a small amount of fluid in the Douglas pouch. Contrast-enhanced computed tomography scan examination was performed through the abdomen, from the domes of the diaphragm to the pubic symphysis. Computed tomography scan depicted a diffusely thickened appendiceal wall, with enlargement of the appendix and a low-density (35 Hounsfield Units) intraluminal mass (Fig. 1b). The patient underwent laparoscopic appendectomy, and the post-operative course was unremarkable.

At the pathological examination the resected appendix was thickened and stiffened (Fig. 2a). Histology revealed multiple neurofibromas in the muscular layer, submucosa and mucosa of the appendix, and immunohistochemical examination showed positive staining for S-100 (Fig. 2b). The presence of S-100 expression by immunohistochemistry along with the clinical findings were diagnostic of appendiceal neurofibroma.

Fig. 1. (a) Multiple, extensive neurofibromas were visible on the skin of the abdomen; (b) abdominal computed tomography scan revealing an enlarged and diffusely thickened appendix with a low-density intraluminal mass (blue arrow).

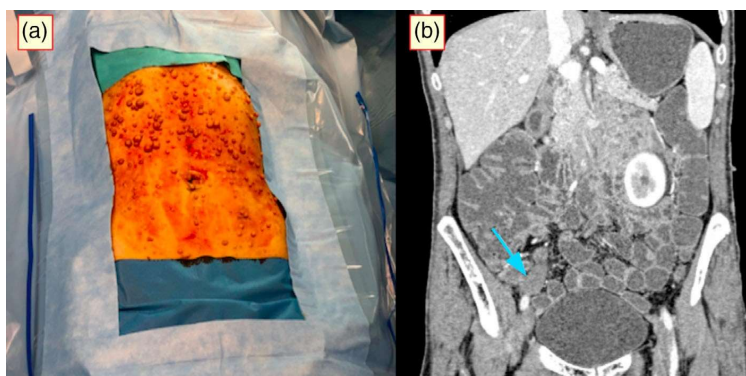
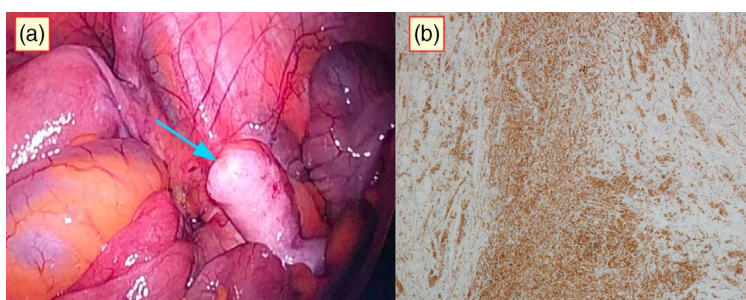


Fig. 2. (a) Intra-operative view of a diffusely thickened and stiffened appendix (blue arrow); (b) immunohistochemistry examination showed immunohistochemical staining positive for S-100.



Neurofibromatosis type 1 (NF-1), also known as von Recklinghausen's disease, is an autosomal dominant hereditary syndrome that can affect tissues of neuroectodermal and mesenchymal origin. It is associated with variable clinical presentations, including café-au-lait macules, cutaneous or subcutaneous neurofibromas, optic glioma, Lisch nodules and bony dysplasia. The prevalence of NF-1 is 1:4–5000, with an incidence of 1:3000 births.

It is caused by heterozygous mutations in the NF-1 gene on chromosome 17q11.2, which result in the inactivation of the neurofibromin, a guanosine triphosphatase-activating protein (GTPase) with tumour suppressor function that negatively regulates RAS/mitogen activated protein kinase pathway activity.

Clinical presentation depends on the nature of mutation, the time when it occurs and if other additional alterations in related genes are present.¹

Gastrointestinal tract involvement is reported in 5–25% of patients with NF-1, but only 5% are symptomatic.^{2,3} Appendiceal neurofibromatosis is an extremely rare manifestation of NF-1.⁴

Appendectomy is the standard treatment for appendiceal neurofibromas and is aimed at preventing complications, improving symptoms and avoiding the potential risk of malignant transformation.⁵

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