Capturing venous thromboembolism: imaging and outcomes of venous thromboembolism

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CHAPTER 10

Measuring quality of life after pulmonary embolism

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Abstract

Patients may experience a spectrum of complications and long-term sequelae following acute pulmonary embolism (PE), which can affect physical and psychosocial functioning as well as psychological well-being, causing a considerable impact on patients' daily functioning and quality of life (QoL). Improved understanding of the impact of the acute PE event as experienced by patients can be achieved through the measurement of QoL. As a more holistic approach to capturing well-being, assessing QoL presents the opportunity to quantify and monitor the impact of the PE diagnosis on patients' lives. Measurement of QoL could also help identifying the needs of individual patients and guide patient-tailored care. Patient-reported outcome measures (PROMs) are ideal tools to provide insight into the patient's perception of the various aspects of health and well-being. In this chapter, we discuss why, how, and when to measure QoL after acute PE.

Introduction

A spectrum of complications and long-term sequelae can be experienced by patients after an event of acute pulmonary embolism (PE).[1-8] Recurrent venous thromboembolism (VTE) and bleeding complications are the traditionally measured health-care indicators, as is survival. These three commonly recognized outcomes, however, do not capture the entire impact of PE on patients. A broader spectrum of consequences and health effects can occur, causing a considerable impact on the lives of patients. Acute PE and its sequelae affect both physical functioning and psychological well-being, and with that may substantially lower quality of life (QoL).[9-14] Also, an association between VTE and excess health care costs and increased risk of permanent work-related disability has been demonstrated, which underlines the social impact and consequences of the condition.[15,16]

Assessment of QoL following acute PE can contribute to a better understanding of the impact and consequences of PE that patients experience in their daily functioning. Identifying patients' needs based on their QoL will help guide the management of PE and facilitate patient-tailored treatment. Furthermore, monitoring quality of life in addition to other outcome measures over time provides a key opportunity to improve the outcomes of care. In this chapter, we describe why, how, and when to measure QoL after PE.

Assessment of long-term consequences (*Why*)

More than half of patients who experience acute PE report decreased QoL, functional limitations, and/or persistent dyspnea during long-term follow-up.[7] The combination of dyspnea, functional impairment or reduced QoL, with or without measurable limitations of cardiac or pulmonary function after PE without alternative explanation is called the post-PE syndrome.[7] The impact of post-PE syndrome was studied in a cross-sectional study, in which 47% of patients reported persistent dyspnea after a median duration of 3.6 years since PE diagnosis.[17] Patients who had symptoms of dyspnea had reduced exercise capacity according to 6-minute walking test and impaired QoL compared to patients without dyspnea.[17] The largest differences between patients with and without dyspnea were observed in three specific QoL dimensions (based on the Pulmonary Embolism Quality of Life [PEmb-QoL] questionnaire): "frequency of complaints", "intensity of complaints", and "social limitations" evaluating to what extent the symptoms interfere with patients' usual social activities.[17] These findings suggest that patients with persistent dyspnea also have other symptoms, such as pain or a feeling of pressure in the chest, and experience limitations in their daily social activities and functioning. In another study evaluating QoL after PE, 47% of patients reported persistent dyspnea at 6-month follow-up after the acute PE and 25% were diagnosed with post-PE impairment, which was defined as a combination of one or more echocardiographic abnormalities indicating right ventricle dysfunction and at least one of the clinical, functional and/or laboratory parameters of right ventricle failure.[10] Diagnosis of post-PE impairment at 6 months was associated with decreased QoL based on "work-related problems", and QoL was affected by severe dyspnea defined as New York Heart Association (NYHA) class III or IV. Also in other studies, associations between dyspnea, reduced QoL and decreased exercise capacity have been observed.[18-20] Since the post-PE syndrome is a common long-term consequence among survivors of acute PE, reported in up to 40-60% of PE survivors, monitoring QoL, functional status and persistent symptoms that are suggested to be drivers of impaired QoL, such as dyspnea, in all patients who experienced PE will contribute to the identification of those who may benefit from targeted interventions such as cardiopulmonary rehabilitation.[21, 22] In a scoping review aiming to understand the impact of VTE from the patient perspective, one of the major themes identified by the authors was "Loss of self: life is changed".[23] This theme captured the effects of VTE on different aspects of daily life, including work, school, sports, family and social activities, leading to a global reduction in QoL. Adequate assessment of QoL is crucial to quantify and monitor the impact of the PE diagnosis on patients' lives and provide appropriate care.

Moreover, a negative impact of acute PE on mental and social well-being has been demonstrated. Several qualitative studies showed that the experience of a VTE was life changing for patients and that they felt that the VTE event was a defining moment in their life or that they were no longer able to lead their normal life.[12, 13, 24] Patients also described to experience emotional and psychological distress triggered by hypervigilance to reminders of the VTE, fear of recurrence, panic and uncertainty.[12, 24] Diagnosis of depression has been reported in 16% of patients at 6 months following the acute PE, and mild to severe symptoms of anxiety and depression were reported in up to 30% of patients after 12 months and in 19-24% of patients up to 2 years after PE.[8, 10, 25, 26] After 3 years of follow-up, patients with VTE were still found to have a more than two-fold increased risk of depression compared to the general population.[27] Persistent symptoms including dyspnea and limitations in daily functioning were associated with depression and anxiety.[25, 28] Furthermore, physical and psychological symptoms during the recovery of PE also affected social life, leading to changes in social relationships.[29] Both patients and the people surrounding them were affected by anxiety and efforts to reengage in everyday life after the acute PE event.[30] In turn, high depression scores were associated with poorer physical and mental QoL [31] and patients reported to experience symptoms of anxiety and depression as major impairment after PE.[13] Measuring QoL provides the opportunity to identify and target problems in the mental and social health dimensions.

The prognosis and outcomes of VTE may differ between women and men. Data from the PREFER in VTE registry demonstrated that women had lower QoL scores, measured using the EuroQoL 5-dimension 5-level (EQ-5D-5L) visual analogue scale (EQ-VAS), than men after 6 months following a first episode of acute PE.[32] Moreover, data from the Home Treatment of Pulmonary Embolism (HoT-PE) study and Follow-Up after Acute Pulmonary Embolism (FOCUS) study showed that the female sex was associated with poorer QoL at 3 and 12 months of follow-up, and in the Evaluation of Long-term Outcomes after Pulmonary Embolism (ELOPE) study, female sex was an independent predictor of reduced QoL improvement over time during 1-year follow-up.[11, 19, 33] Awareness of such differences may provide important insights regarding the health effects that patients may experience during follow-up after acute PE, which can guide management.

An issue that care providers should be aware of during treatment and follow-up of women who experienced PE is abnormal menstrual bleeding associated with anticoagulation. Following an acute VTE event, women can experience a considerable negative impact on QoL caused by abnormal uterine bleeding. Two-thirds of women who start on anticoagulant therapy for acute VTE were found to experience heavy menstrual blood loss**,** which negatively impacted QoL, both over time as well as compared to a control group of women who did not receive anticoagulation.[34, 35] The decrease in QoL over time was most pronounced in women who did not have abnormal menstrual bleeding in the last menstrual period before VTE diagnosis, based on pictorial blood loss assessment chart score, and thus experienced new-onset abnormal menstrual bleeding after the VTE.[34] Women affected by heavy menstrual bleeding reported a significant negative impact on their social life and mental health.[36]

To evaluate which outcomes are most important to patients and combine these in a core set for use in clinical practice, an international working group worked on the development of a standardized set of patient-centered outcome measures for patients with VTE in collaboration with the International Consortium for Health Outcomes Measurement (ICHOM).[37] During this multidisciplinary ICHOM-VTE project, a working group consisting of 2 patient representatives and 25 VTE experts and a project team convened through 9 video conferences between January 2021 and February 2022. Relevant outcomes and outcome measures were identified from the literature after extensive literature searches performed by the project team. Using a modified Delphi process, the working group selected the outcomes that matter most to patients and included these in the standardized set along with the optimal outcome measures to assess the outcomes. QoL was one of the core outcomes most important to patients that was selected to be included in the set. The full ICHOM-VTE set is summarized in **Table 1**.

Since measurement of outcomes in clinical VTE trials is inconsistent across studies and does not include all outcomes that are important, the venous thromboembolism core outcome set (VTE-COS) project (ongoing; July 2019 – December 2023) will define a standardized set of outcomes most important to patients, specifically for use in clinical VTE trials.[38]

Quality of life assessment (*How*)

To understand the impact of acute PE from the patient's perspective, the use of patient-reported outcome measures (PROMs) is the optimal approach. In a position paper of the European Society of Cardiology (ESC), endorsed by the European Respiratory Society (ERS), the routine use of outcome measures to assess QoL and functional outcome is advocated to early identify patients with post-PE syndrome.[21] Also, in a communication of the International Society on Thrombosis and Haemostasis (ISTH), Scientific and Standardization Committee (SSC) Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease, recommendations for the use of PROMs during clinical follow-up of VTE patients are proposed, along with priorities for future studies to optimize PROMs for VTE and evaluate the impact of implementation and use of PROMs on outcomes.[40] Currently, available outcome measures to assess QoL in patients who experienced PE include generic and disease-specific questionnaires. Generic PROMs assess general aspects relevant to a broad range of patient groups allowing comparisons across conditions, settings and populations, while disease-specific PROMs capture aspects of health relevant to a specific patient group or condition and typically have greater face validity.[41-44]

The generic questionnaires which are most frequently used in VTE patients are the EuroQoL 5-dimension (EQ-5D) instrument and 36-item Short Form Health Survey (SF-36), both widely used in several conditions.[45-49] The EQ-5D questionnaire covers the five dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and a Visual Analogue Scale (VAS) to assess general health status on a scale from 0 to 100 (worst to best imaginable health state).[49] The 36 items of the SF-36 instrument assess functional, social and mental health status, and general health perceptions in eight dimensions.[46] A physical component summary score and mental component summary score can be calculated.

Table 1: The ICHOM-VTE set of patient-centered outcomes.[37]

	Outcomes	**Outcome measures**
Patient-reported outcomes	Quality of life	PROMIS Scale v1.2 - Global Health PEmb-QoL questionnaire VEINES-QOL questionnaire
	Functional limitations (including ability to work)	Post-VTE Functional Status scale
	Pain (including symptom severity)	PROMIS Short Form v2.0 - Pain Intensity 3a
	Dyspnea (including symptom severity)	PROMIS Short Form v1.0 - Dyspnea Severity 10a
	Psychosocial well-being	Patient Health Questionnaire (PHQ-9) Generalized Anxiety Disorder (GAD-7)
	Satisfaction with treatment	Single question: "Are you satisfied with your VTE treatment?" Yes/No If answer to the single question is 'No': Anti-Clot Treatment Scale (ACTS)
	Changes in life view	Single question: "Have you experienced a change in your expectations, aspirations, values, or perspectives on life opportunities since the diagnosis of VTE?" Yes/No
Long-term consequences of disease	Use of health-care resources	Number of hospital stays and length of stay; number of emergency room visits; number of non-hospital health-care activities (including general practice, outpatient clinic visits, home health care, and rehabilitation)
	Chronic thromboembolic pulmonary hypertension	Clinical diagnosis
	Chronic thromboembolic pulmonary disease	Clinical diagnosis
	Post-thrombotic syndrome	Villalta Score
Disease-specific complications	Recurrence	Has the patient had recurrent venous thromboembolism according to the ISTH definition? Yes/No
	Survival	Death regardless of cause
Treatment-related complications	Bleeding	Did the patient have any bleeding that was worrisome to the patient or the clinician, impacted daily activities or required medical treatment? Yes/No
	Procedure-related complications	Has the patient experienced an undesirable and/or unintended outcome that is a direct result of a procedure? Yes/No

The patient-reported outcomes are assessed using patient-reported outcome measures. The long-term consequences of disease, disease-specific complications, and treatment-related complications are health-care professional-reported and primarily defined according to the International Society on Thrombosis and Haemostasis (ISTH) Common Data Elements for venous thromboembolism.[39]

Abbreviations ICHOM: International Consortium for Health Outcomes Measurement, VTE: venous thromboembolism, PROMIS: Patient-Reported Outcomes Measurement Information System, PEmb-QoL: Pulmonary Embolism Quality of Life, VEINES-QOL: Venous Insufficiency Epidemiological and Economic Study–Quality of Life, ISTH: International Society on Thrombosis and Haemostasis.

The only disease-specific instrument available for the evaluation of QoL following PE, is the PEmb-QoL questionnaire.[44, 50, 51] The instrument consists of 40 items covering 6 dimensions: frequency of complaints, limitations in activities of daily living, work-related problems, social limitations, intensity of complaints, and emotional complaints.[50, 52] The PEmb-QoL questionnaire was validated in a study population of patients with a history of acute PE and shown to be a reliable instrument to specifically assess QoL after PE, having adequate internal consistency, test-retest reliability, and convergent validity as supported by the observed correlation with the SF-36 questionnaire.[52]

The PEmb-QoL questionnaire has been translated into several languages. Validation studies of translated versions of the instrument demonstrated the reliability, reproducibility, and validity of the translations.[10, 53-57] To interpret changes or differences in QoL and assess clinically relevant change, meaningful to patients, the minimal clinically important difference (MCID) for the PEmb-QoL questionnaire was determined.[58] This supports the interpretation of changes in PEmb-QoL scores and could support taking appropriate action based on relevant changes in health status.

Outcome measures of QoL are not only relevant and useful in clinical practice, QoL assessment is also incorporated in studies which include QoL as a primary or secondary outcome. Several studies, both cohort studies and cross-sectional studies, have been performed with the primary objective to evaluate QoL after acute PE.[9, 20, 59, 60] QoL can be used to assess the effectiveness of treatments or can be quantified or monitored during follow-up in observational studies. The study protocol of the FOCUS study, in which a large multicenter prospective cohort of all-comers with symptomatic acute PE was followed over a period of 2 years, for instance, included disease-specific and generic QoL during follow-up measured using the PEmb-QoL questionnaire and 5-level EQ-5D instrument as one of the secondary outcomes.[8, 61]

Timing of measuring quality of life (*When*)

During the first year after acute PE, QoL improvement has been observed.[11, 19, 60] In low-risk PE patients who were early discharged, QoL measured using the PEmb-QoL questionnaire and EQ-5D-5L improved between 3 weeks and 3 months after PE.[33] During 1-year follow-up, physical and mental component summary scores of SF-36 and PEmb-QoL score improved from baseline to 12 months, with the greatest improvement in the first 3 months after acute PE and more modest improvement observed from 6 to 12 months.[19] These findings suggest that measurement of QoL at 3 and 6 months after PE diagnosis is insightful to monitor recovery and identify improvement or reduction in QoL.

During the ICHOM-VTE project, the timepoints proposed to measure the outcomes in the standardized set were also identified using the Delphi consensus method.[37] The start of the timeline, defined by the index event as “anchor” which helps to plan the subsequent timepoints, and the measurement timepoints during follow-up were determined during the Delphi process. The index event was defined as confirmation of the VTE diagnosis, as was discussed to not rely on hospitalization or start of anticoagulant therapy since not all patients with VTE are admitted to the hospital or receive immediate anticoagulant therapy, for instance due to active bleeding or high risk of bleeding. Considerations in defining the timepoints during follow-up included recommendations of the current guidelines regarding clinical evaluation of patients after the acute VTE episode and the recommended treatment phase, the duration of follow-up after VTE as (routinely) applied in different countries, and the period of at least 3 months of effective anticoagulant treatment after which long-term complications such as chronic thromboembolic pulmonary hypertension (CTEPH) can be diagnosed. First measurement of outcomes at baseline enables to capture change during follow-up after the acute event. In addition to the baseline timepoint, a 3-month timepoint and 6-month timepoint after VTE diagnosis were included in the standardized set, in line with the insights based on study findings. Also, a 1-year timepoint followed by ongoing measurement on a yearly basis, relevant for as long as the patient is under care, was included in the ICHOM-VTE set. The set provides a clear timeline for measurement of QoL during follow-up of patients after PE.

Conclusion

There is a broad spectrum of consequences and health effects which can occur after acute PE. Persistent dyspnea, reduced functional status and/or impaired QoL are experienced by more than half of PE survivors during long-term follow-up, and PE has been shown to have a considerable negative psychological and social impact. Measuring and monitoring QoL in routine clinical practice can reveal limitations in health domains, which is valuable during management and follow-up after PE and will guide facilitating treatment for those who may benefit from interventions, for instance to target persistent symptoms or mental health problems. Furthermore, during the Delphi process in the course of the development of a core set of patient-centered outcomes for patients with VTE for use in clinical practice, QoL was identified as one of the health outcomes that matter most to patients – a finding that underlines the value of measuring QoL. QoL can be assessed using patient-reported generic or disease-specific questionnaires, which are ideal tools to provide insight into the various dimensions of health perceived by the patient and can help improve understanding of the impact of acute PE on patient lives. Insights gained from studies and findings of the Delphi consensus analysis conducted during the development of the standardized outcome set for use in clinical practice, provide guidance on when to measure quality of life during follow-up after acute PE.

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