Original Article

Development and Initial Validation of a Questionnaire to Measure Health-Related Quality of Life of Adults with Common Variable Immune Deficiency: The CVID_QoL Questionnaire

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What is already known about this topic? Quality of life (QoL) is poor in patients with common variable immune deficiency (CVID).

What does this article add to our knowledge? A single questionnaire to assess the burden of disease in patients affected by CVID was developed and initially validated.

How does this study impact current management guidelines? The CVID_QoL is a disease-specific tool to quantify the burden of disease. The emotional, relational, and clinical aspects of QoL in adult patients with CVID may be captured by the new tool potentially useful in the clinical assessment.

BACKGROUND: Generic health status quality of life (QoL) instruments have been used in patients with common variable immune deficiency (CVID). However, by their nature, these tools may over- or underestimate the impact of diseases on an individual's QoL.

OBJECTIVE: The objective of this study was to develop and validate a questionnaire to measure specific-health-related QoL for adults with CVID (CVID_QoL).

METHODS: The 32-item content of the CVID_QoL questionnaire was developed using focus groups and individual patient interviews. Validation studies included 118 adults with CVID who completed Short Form-36, Saint George Respiratory Questionnaire, General Health Questionnaire-12, and EuroQol-5D questionnaire in a single session. Principal component and factor analysis solutions identified 3 scores to be similar in number and content for each solution. Validation of 3 factor scores was performed by construct validity. Reproducibility, reliability, convergent validity, and discriminant validity were evaluated. Matrices consisting of correlations between the 32 items in the CVID_QOL were calculated.

RESULTS: Factor analysis identified 3 dimensions: emotional functioning (EF), relational functioning (RF), and gastrointestinal and skin symptoms (GSS). The instrument had good internal consistency (Cronbach's alpha, min. 0.74 for GSS, max. 0.84 for RF, n = 118) and high reproducibility (intraclass correlation coefficient, min. 0.79 for RF, max 0.90 for EF, n = 27). EF and RF scores showed good convergent validity correlating with conceptually similar dimensions of other study scales. Acute and relapsing infections had a significant impact on EF and RF.

CONCLUSIONS: This study provides evidence of the reliability and construct validity of the CVID_QoL to identify QoL issues in patients with CVID that may not be addressed by generic instruments. **(J Allergy Clin Immunol Pract 2016;■:■-■)**

Key words: *Burden of disease; Common variable immune deficiency; CVID_QoL; Disease-specific questionnaire; Quality of life; Questionnaire validation*

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Abbreviations used
BMI- Body mass index
CVID- Common variable immune deficiency
EF- Emotional functioning
EQ-5D- EuroQol-5 dimensions questionnaire
GHQ-12- General health questionnaire
GSS- Gastrointestinal and skin symptoms
ICC- Intraclass correlation coefficient
MCS- Mental component summary
PAD- Primary antibody deficiency
PCS- Physical component summary
PhGA- Physician global assessment
PtGA- Patient global assessment
QoL- Quality of life
RF- Relational functioning
SF-36- Short Form 36 questionnaire
SGRQ- Saint George Respiratory Questionnaire
TL- Trough levels
VAS- Visual analog scale

Primary antibody deficiency (PAD) is an umbrella term encompassing a broad array of primary immunodeficiency diseases collectively characterized by a quantitative and/or qualitative impairment of antibody production. Common variable immune deficiency (CVID) is the most common symptomatic form of PAD.[1] CVID includes a heterogeneous group of antibody deficiencies mostly of unknown etiology, frequently diagnosed in adults. Across the spectrum of clinical manifestations, patients are frequently affected by severe and recurrent infections, autoimmune disorders, granulomatous and inflammatory diseases, and cancers.[2]

Improvements in awareness, prompt diagnosis, and the introduction of immunoglobulin replacement therapy have resulted in substantially extended life expectancy for patients with PAD.[3-5]

Owing to this extended life expectancy, the qualitative patient experience, frequently conceptualized as "quality of life" (QoL), has become an important focus of clinical care and outcomes research.[6] QoL is a multidimensional concept that encompasses the physical, psychological, and social aspects of well-being. Central to this is that an individual's perception of the impact of illness on his/her life is often as important as (if not more important than) clinical factors in predicting morbidity and mortality.[7] Formal QoL assessments, often made by administering patient-completed questionnaires, have become a ubiquitous part of intervention and patients' outcome research, and are essential to guide efforts to optimize the quality and outcomes of clinical care.

Many QoL measurement instruments (or "tools") are available and the decision to use one over another tool, to use a combination of 2 or more tools, should be driven by the purpose of the measurement. The choice will depend on a variety of factors including the characteristics of the population (eg, age, economic status, language/culture), the environment in which the measurement is undertaken (eg, clinical trial, routine physician visit), and on the purpose of the assessment (eg, measuring changes over time as in a natural history study vs clinical use to provide a snapshot to supplement physician impression vs as an endpoint to evaluate the effect of an intervention). These tools are essentially used for research purposes, and very few initiatives introduced such instruments in the clinical routine.

To our knowledge, mainly generic health status QoL instruments have been used in adult populations affected by CVID, and among them the Medical Outcomes Study in the Short Form (SF-36 or SF-12) and the General Health Questionnaire-12 Items (GHQ-12).[8-10] However, generic QoL instruments, by their nature, only include questions applicable to a wide variety of populations and disease states, and may over- or underestimate the true impact of CVID on an individual's QoL.

The use of disease-specific tools is desirable to provide a more accurate picture of the burden of each disease. Although disease-specific tools have been developed for a variety of illnesses,[11-13] to our knowledge, there have been no studies to develop and rigorously evaluate a disease-specific instrument for use in CVID patient populations. Tools validated for other conditions such the Saint George Respiratory Questionnaire (SGRQ) in use for patients with lung diseases have been used in patients with CVID.[14] To address this need, our aim was to develop and validate an acceptably short, cross-culturally valid, and reliable instrument to measure QoL in adults with CVID.

METHODS

This single-center study was carried out in the Clinic for Adult Immune Deficiency of Rome, Italy. Eligible patients were adults aged 18 years or older, with a diagnosis of CVID[15] established 6 or more months before enrollment and currently receiving intravenous or subcutaneous immunoglobulin replacement therapy. Exclusions included inability or unwillingness to provide written informed consent or significant medical or psychiatric illness that, in the opinion of the treating clinician, precluded participation. All patients enrolled provided their informed consent. The Ethical Board of the Sapienza, University of Rome approved this study. The portion performed at Texas Children's Hospital was approved by the Institutional Review Board for the protection of human subjects at Baylor College of Medicine. The study design is summarized in Figure 1.

Instrument development

The content of the CVID_QoL questionnaire was based on qualitative focus groups and individual patient interviews conducted in the clinic for primary immune deficiencies in Rome. Three independent focus groups were managed with patients with CVID (including a total of 28 patients) and an expert panel consisting of a nurse, a doctor, and a psychologist, each with expertise in primary immunodeficiency care. These sessions elicited an open discussion of the most relevant issues affecting the patient's personal experience with disease. A list of 56 items thought to be of most concern to patients was assembled. The number of items was reduced to 32 after ranking items in descending order and selecting the highest-ranking items for inclusion. Study psychologists conducted structured interviews with other patients with CVID recruited in 2 consecutive days (5 patients per day) who had not participated in any of the focus groups to evaluate general readability of each item and its answer choices and to refine the wording and order of the questions. In the final questionnaire, negatively worded items were avoided and response options were formulated using a 5-point scale, with 0 = "never" and 4 = "always," with higher values generally indicating increasing disability. The final version of the CVID_QoL questionnaire is shown in Figure E1 (available in this article's Online Repository at www.jaci-inpractice.org).

An English translation of the questionnaire was also obtained following the 3 phases described by the guidelines for the translation and cultural adaptation of health-related QoL measures.[16,17] During