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;4:1169-79)**

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

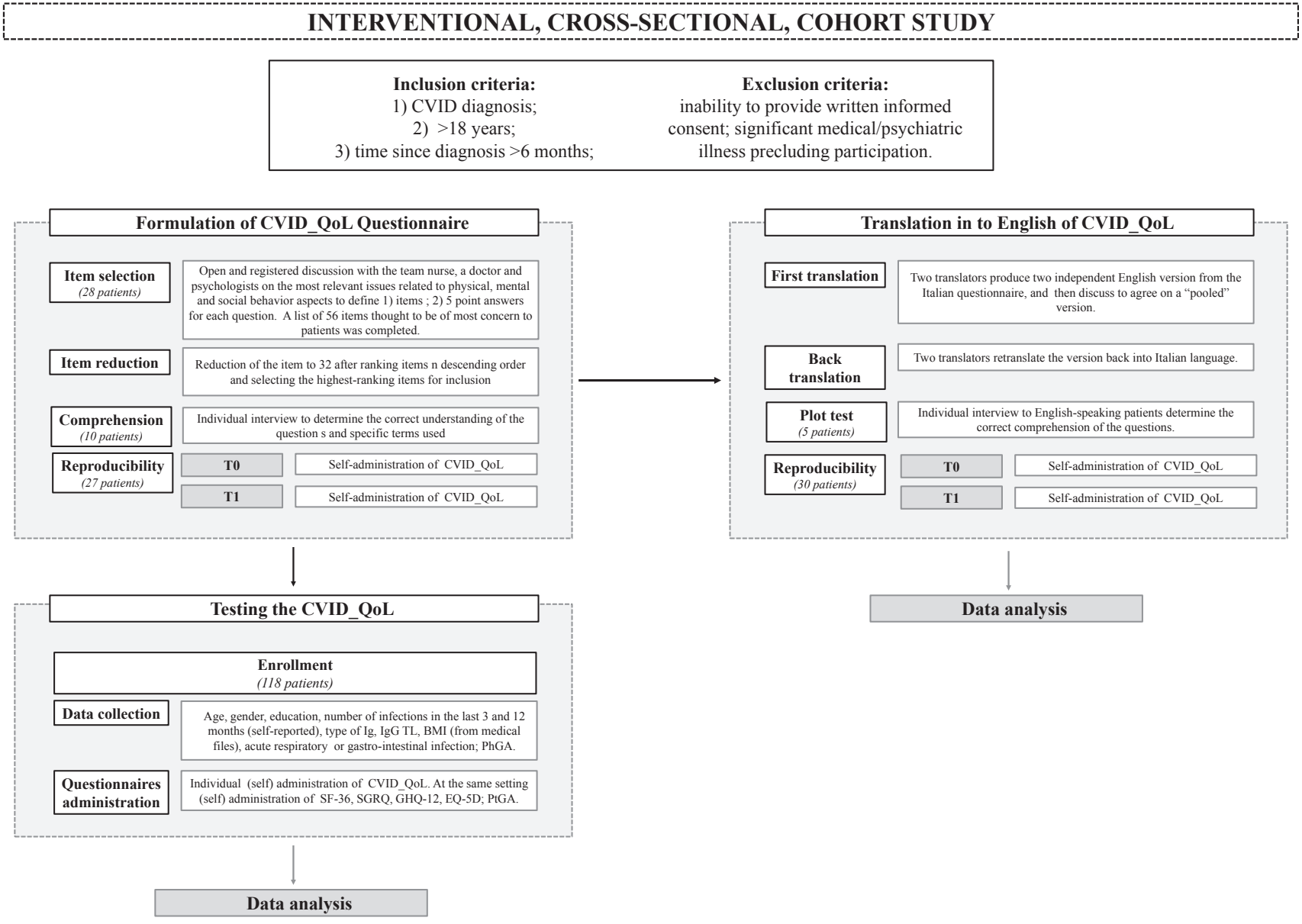

FIGURE 1. Study design to develop and validate a questionnaire to measure health-related quality of life of adults with common variable immune deficiency. *BMI*, Body mass index; *CVID*, common variable immune deficiencies; *EQ-5D*, EuroQol-5 dimensions questionnaire; *GHQ-12*, Global Health Questionnaire; *PAD*, primary antibody deficiency; *PtGA*, patient global assessment; *QoL*, quality of life; *SF-36*, Short Form 36 questionnaire; *SGRQ*, Saint George Respiratory Questionnaire; *TL*, IgG trough level.

phase 1, 2 English mother-tongue translators produced 2 independent versions, which were compared and discussed to agree on a "pooled" version. In phase 2 (back-translation), 2 independent translators retranslated the version back into the original language, without having access to the original version. Phase 3 involved administering the questionnaire to 5 English-speaking patients with CVID enrolled from the adult CVID population followed at Texas Children's Hospital, to assess comprehension of each translated item. The English version of the CVID_QoL questionnaire is shown in Figure E2 (available in this article's Online Repository at www.jaci-inpractice.org). The validation process did not include the 5 English-speaking patients with CVID. Further studies in progress will allow for the analysis of the cross-cultural validity of the English version of the CVID_QoL instrument.

Instrument validation

To validate the questionnaire, established adult patients with CVID not involved in the focus groups nor in the preliminary structured interviews were recruited from the entire cohort of adult CVID clinics in Rome, Italy, between January and April 2015 (Figure 1). One hundred and twenty-seven patients with CVID considered eligible for the study were consecutively approached; nine declined to participate. To evaluate reproducibility, 27 patients were randomly selected to complete the measures in a desired time frame of 20-30 days after baseline.

Demographic and clinical characteristics

Participants reported demographic characteristics, including age, sex, and highest level of education completed. They were also asked to report the number of infections they had experienced within the 3 and 12 months before participation. Clinical data were abstracted from the medical record, including the date of CVID diagnosis (used to calculate duration of disease), immunoglobulin levels at the time of diagnosis, IgG trough levels (TL), current body mass index (BMI), presence of bronchiectasis by computed tomography scan, and chronic diarrhea defined as abnormal frequency and fluidity of fecal evacuations lasting more than 1 month in the year preceding the study.[18]

The reported number of infections within the previous 3 and 12 months was cross-validated by clinicians' review of clinical records. The physicians also rated their perception of disease severity for each patient at the time of the evaluation (physician global assessment, or PhGA).

Questionnaires

After providing informed consent, patients completed questionnaire packets including the following questionnaires administered in this sequential order: CVID_QoL, the SF-36, the SGRQ, the GHQ-12, the EuroQol-5 dimensions questionnaire (EQ-5D), and a patient global assessment (PtGA). All participants were given the questionnaires to complete in the clinic waiting room before meeting with their physician.

SF-36. The SF-36 questionnaire is a self-administered questionnaire; it includes 36 items in a Likert-type or forced-choice format and measures health on 8 multi-item dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.[19] Scores for each dimension range from 0 to 100, with higher scores indicating better health. Two summary measures, the physical component summary (PCS) and mental component summary (MCS), cross-culturally validated in the framework of the International QoL Assessment project for the Italian version of the SF-36 were generated.[20] Because SF-36 is designed to assess the deterioration of the health status, we expected to observe inverse correlations with the CVID_QoL items.

SGRQ. The SGRQ is a self-administered, 50-item questionnaire that measures the respiratory-specific health status.[21] The items are divided into 3 dimensions: "symptoms," "activities," and "impacts" of disease on activities of daily living. The total score and individual dimension score range from 0 to 100. The higher the score, the worse the QoL.

GHQ-12. The GHQ-12 is a self-administered, 12-items questionnaire, designed to measure psychological distress and to detect current nonpsychotic, psychiatric disorders, such as depression and anxiety.[22] Answers are given on a 4-point scale. When scored with the binary method (0−0−1−1), the GHQ-12 can be used as a screening tool yielding final scores that range from 0 to 12. Operationally, patients scoring 4 or more were considered as "GHQ-positive (GHQ+)"/at risk of anxiety and depression.[23]

EQ-5D. The EQ-5D is a self-administered questionnaire, consisting in a descriptive system with 5 dimensions ("mobility," "self-care," "usual activities," "pain/discomfort," "anxiety/depression") and a visual analog scale (VAS).[24] In the descriptive system, for each dimension, the answers are coded with a 1-digit number from "1" ("no problems") to "5" ("extreme problems"). The digits of the 5 dimensions are combined into a 5-digit number, which describes the overall health state of the respondent.[25] The EQ VAS is a VAS with endpoints labeled "the best health you can imagine" ("100") and "the worst health you can imagine" ("0"): subjects had to write the number marked in the scale on a box.

Physician and patient global assessments. The PhGA and the PtGA consisted of the following questions respectively: for PhGA "In your opinion, compared to other patients with the same condition, how severe is the disease of patient X?" and for PtGA "In your experience, how severe is your disease?". Answers were given on a 5-point scale from 0: "very mild," 1: "mild," 2: "moderate," 3: "severe," and 4: "very severe." The PhGA was completed by the physician at the end of the clinical outpatient visit. The PtGA was completed, as were other questionnaires, before meeting the physician.

Analyses

Patient demographics and clinical characteristics are summarized by frequencies and percentages, and means and standard deviations where appropriate.

We generated descriptive, comparative analyses of CVID_QoL Global scores by demographic and clinical characteristics of study participants. The CVID_QoL Global score was defined as the sum of all scores of each item (possible range: 0-128), and it was transformed as a percentage of the maximum possible score. For example, a score of 64 would correspond to 50 on the transformed scale. The same transformation, eventually, was performed for all the dimensions resulting from the factor analysis. When up to 3 answers were missing in a given dimension, the score of the missing items was imputed as the average scores of the items in the same dimension. When more than 3 items in the same dimension were missing, the whole dimension was considered as missing.

We evaluated the factorial structure of the CVID_QoL to identify the main dimension underlying the items. For the factor analysis, we utilized the principal component method and principal axis factoring and determined how many factors to extract using Cattell's screen test.[26,27] Reproducibility by the intraclass correlation

TABLE I. Comparisons of mean values of CVID_Qol Global, EF, RF, GSS scale scores by categories of patient characteristics for 118 adult patients with CVID

	n (%)	CVID_QoL Global	Emotional functioning (EF)	Relational functioning (RF)	Gastrointestinal and skin symptoms (GSS)
Sex					
Male	46 (39)	25.7 (14.2)	28.5 (15.9)	20.4 (13.1)	24.2 (19.5)
Female	72 (61)	31.3 (16.4)	34.4 (17.6)	26.4 (19.2)	27.5 (21.9)
P value		*ns**	*ns**	*ns**	*ns**
Age					
≤ 50 y	66 (56)	26.5 (15.5)	29.3 (17.4)	21.4 (15.9)	24.6 (20.3)
> 50 y	52 (44)	32.6 (15.7)	35.7 (16.4)	27.5 (18.4)	28.2 (21.8)
P value		.04*	.04*	*ns**	*ns**
BMI					
≤18.5	9 (7)	41.1 (11.4)	47.8 (12.3)	31.5 (16.7)	40.3 (22.1)
18.6-24.9	67 (57)	28.2 (15.8)	31.0 (16.4)	24.2 (17.3)	24.2 (22.5)
≥25	42 (36)	28.0 (15.9)	31.1 (18.3)	22.3 (17.7)	26.5 (17.1)
P value		.02†	.004†	*ns*†	.05†
Highest level of education completed					
<13 y	31 (26)	32.1 (17.5)	35.2 (19.4)	28.3 (19.9)	25.9 (17.3)
≥ 13 y	87 (74)	28.3 (15.3)	31.2 (16.5)	23.0 (16.3)	26.6 (22.2)
P value		*ns**	*ns**	*ns**	*ns**

BMI, Body mass index; *CVID*, common variable immune deficiency; *ns*, not statistically significant; *QoL*, quality of life.
CVID_QoL Global, EF, RF, and GSS scores expressed as percentages were presented as mean (SD).
**P* values were calculated by the *t*-test.
†*P* values were calculated by ANOVA.

coefficient (ICC) for all dimensions was evaluated. Reliability of the CVID_QoL by using Cronbach's alpha and Pearson's correlation and convergent validity by examining Pearson's correlations between the CVID_QoL Global, CVID_QoL dimensions scores, and existing QoL measures were evaluated. Discriminant validity was assessed by comparing scores between subsets of patients. CVID_-QoL scores between groups with chronic diarrhea against those without diarrhea were evaluated by Student's *t*-test. We also compared CVID_QoL scores between patients grouped according to the number of infectious episodes within 3 (0-1, >1) and 12 months (0-1, 2-6, >6) before enrollment, by Student's *t*-test and ANOVA, respectively.

The statistical significance was set at the conventional level of $P < .05$. All statistical analyses were performed using the statistical package Stata 11 (Stata Corp., College Station, Tex) and GraphPad5 (GraphPad software, San Diego, Calif, www.graphpad.com).

RESULTS

Participant characteristics

One-hundred and eighteen consecutive patients with CVID provided informed consent and participated in the study. Demographic data and clinical characteristics are summarized in Table I. The majority of patients were female (n = 72, 61%). The mean duration of disease was 12.1 ± 10.7 years. All patients were on Ig replacement therapy, with 89% receiving intravenous Ig replacement therapy. The mean TL of Ig at the time of the study was 663 ± 158 mg/dL. The average number of reported infections in the 3 and 12 months preceding the test was 1.4 ± 1.5 and 4.2 ± 3.8 episodes, respectively. Patients involved in focus groups and structured interviews had similar demographic and immunological characteristics to the overall CVID cohort attending our center (data not shown).

Instrument characteristics

Feasibility. All (n = 118) patients completed the 32-item CVID_QoL questionnaire, which required approximately 10 to 15 minutes for completion. The missing response rate was 2.0% for all questionnaire items. Table I displays baseline scores by age, sex, and BMI. Patients older than 50 years had significantly worse CVID_QoL Global and emotional functioning (EF) scores. No difference was observed between males and females and between patients with higher or lower education level. Patients with lower BMI (≤18.5) had a higher CVID_QoL Global score in comparison with those having normal and/or high BMI. No correlation was appreciated between the CVID_QoL score and IgG, IgA, and IgM serum levels at diagnosis and IgG TL at the time of the study, suggesting that immunoglobulin serum levels have a low impact on QoL that is a complex measurement influenced simultaneously by many factors.

Factor analysis. Factor analysis (Table II) with varimax rotation yielded a 3-factor model: EF, relational functioning (RF), and gastrointestinal and skin symptoms (GSS), together accounting for 72% of the variance. EF includes 19 items, RF includes 9 items, and GSS includes 4 items. Loadings ranges were EF: 0.31-0.77; RF: 0.34-0.72; GSS 0.33-0.71. Cough was included in the relational dimension (RF), whereas gastrointestinal manifestations and skin diseases went together in a separate dimension (GSS). The CVID_QoL dimensions identified by factor analysis are represented in Figure 2. The average CVID_QoL Global score was 29 ± 16.5%. Scores observed in each dimension were EF: 32.4 ± 17.5% (range: 0% to 82.9%), RF: 17.5 ± 32.4% (range: 0% to 84.4%), GSS: 26 ± 21% (range: 0% to 75%). A total of 32% of patients had a CVID_QoL Global ≤ 20%, 44% had a CVID_QoL Global ranging from 20% to 40%, and 21% had a CVID_QoL Global

TABLE II. Principal component analysis* of the CVID_QoL and loading for the 3 dimensions and for each item

CVID_QoL items	Dimension 1: Emotional functioning (EF)	Dimension 2: Relational functioning (RF)	Dimension 3: Gastrointestinal and skin symptoms (GSS)
1 Sadness	0.61		
2 Dietary changes			0.71
3 Anger	0.41		
4 Diarrhea			0.69
5 Difficulty planning	0.56		
6 Cough		0.34	
7 Unable to provide care		0.58	
8 Health exacerbation	0.77		
9 Joint pain	0.56		
10 Needing help	0.58		
11 Run out of medications/immunoglobulins		0.47	
12 Afraid of an adverse reaction	0.55		
13 Concerned about the future	0.77		
14 Limited by diarrhea			0.68
15 Loss of autonomy	0.61		
16 As contagious		0.68	
17 Difficulty in usual activities	0.52		
18 Fear of death	0.43		
19 Limited by cough		0.72	
20 Isolated		0.57	
21 Fear of illness	0.55		
22 Weakness	0.66		
23 Difficulty in sexual relations		0.59	
24 Bothered by immunoglobulins	0.31		
25 Limitation on leisure activity		0.59	
27 Difficulty in relationships		0.69	
28 Perception as sick	0.72		
29 Embarrassed	0.49		
30 Becoming infected	0.47		
31 Troubled by other patients	0.36		
32 Tired	0.56		

CVID, Common variable immune deficiency; *QoL*, quality of life.
Each item is indicated as the number of the question, followed by an indicative word of the sentence, that is, 1 Sadness: question number 1: I felt sad.
*Principal components method with varimax rotation; rotation converged in 7 iterations.

$\geq$ 40%. The histogram of the distribution of the 118 CVID Global scores is represented in Figure 3.

Reproducibility. There were no significant differences in the first and second assessment scores. Of the 27 patients evaluated for reproducibility, values of agreement were very satisfactory: EF, ICC = 0.90 (95% CI 0.80-0.95); RF, ICC = 0.79 (95% CI 0.59-0.90); GSS, ICC = 0.85 (95% CI 0.71-0.93). All *P* values were <.001.

Reliability. A strong internal consistency of each disease-specific dimensions (>0.7) with an alpha coefficient of 0.82, 0.84, and 0.74 for the EF, RF, and GSS subscales, respectively.

Convergent validity. Correlations between the Global and dimensions of CVID_QoL and those of each of the 5 additional instruments applied to our patients with CVID as well as the instrument dimensions are reported in Table III.

SF-36. Statistically significant correlations were found between the EF dimension and the SF-36 PCS and MCS summary measures (−0.55 and −0.49); the RF dimension and the SF-36 PCS and MCS summary measures (−0.52 and −0.40); and between the GSS dimension and the SF-36 summary score MCS (−0.38).

SGRQ. EF and RF were positively related to the total SGRQ score (0.52 and 0.54, respectively) and to all SGRQ dimensions, showing that the respiratory problems impact the health-related QoL of CVID, as recently demonstrated.[14] As expected, the GSS dimension was not related to the SGRQ score.

GHQ-12. GHQ-12 was strongly related to the EF (0.74), RF (0.50), and GSS (0.33) dimensions.

EQ-5D. The EF, RF, and GSS dimensions were related to EQ-5D VAS (−0.68, −0.52, −0.32). EF and RF were also related to all EQ-5D components (mobility, usual activities, self-care, pain, and anxiety), whereas GSS was related to usual activity, pain, and anxiety dimensions (Table III).

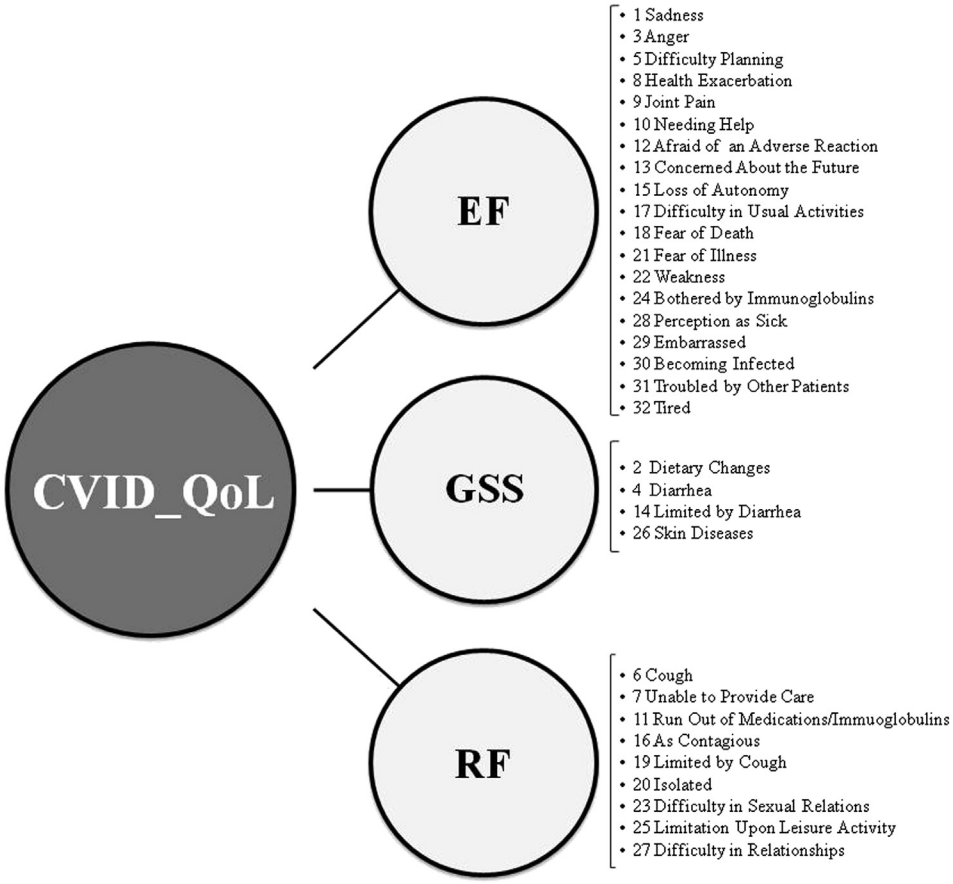

FIGURE 2. CVID_QoL dimensions identified by factor analysis. Each item is indicated as the number of the question, followed by an indicative word summarizing the sentence, that is, 1 Sadness = question number 1: I felt sad. *CVID*, Common variable immune deficiency; *EF*, emotional functioning, *GSS*, gastrointestinal and skin symptoms; *QoL*, quality of life; *RF*, relational functioning.

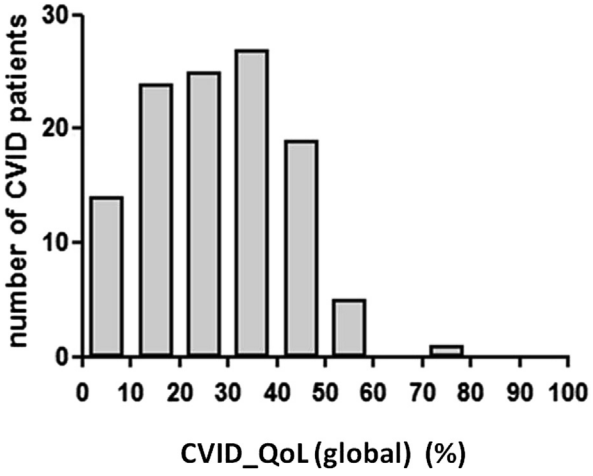

FIGURE 3. Distribution of the 118 CVID_QoL Global scores. Patients were grouped according to their CVID_QoL Global score. *CVID*, Common variable immune deficiency; *QoL*, quality of life.

PhGA and PtGA. A total of 7% of the patients perceived their health status as "very mild/mild," 37% as "moderate," 49% as "severe," and 7% as "very severe." EF, RF, and GSS scores correlated only with PtGA (0.56, 0.43, 0.27). Only RF correlated with PhGA (0.25). As also demonstrated in our previous work,[6] the correlation between PtGA and PhGA was low (0.21).

Discriminatory validity. The experience of acute and relapsing infections had a significant impact on CVID_QoL. Patients reporting a low number of infections (0-1) in the 3 months preceding the study time had lower scores than patients reporting more than 1 infection (Figure 4, *A*). A close relationship between the number of infections and the CVID_QoL scores was even more evident when the number of infections in the year preceding the study was analyzed (Figure 4, *B*). Differently from the Global, EF, and RF scores, the number of infections did not affect the GSS score. This finding was not unexpected in that acute and relapsing infections were mainly respiratory, whereas diarrhea and skin diseases were mainly chronic conditions. Moreover, patients with CVID with chronic diarrhea had a worse CVID_QoL score than patients without chronic diarrhea (36.4 ± 16.0% vs 26.4 ± 15.1%, $P = .004$) and a worse GSS (39.5 ± 20.7% vs 21.6 ± 19.7%, $P < .0001$).

The overall burden of disease was assessed by the analysis of items with the highest and lowest impact on QoL as reported by the entire CVID population. The percentage of patients

TABLE III. Correlations of the CVID_QoL scores with the SF-36, SGRQ, GHQ-12, EQ-5D scores

	CVID_QoL Global	Emotional functioning (EF)	Relational functioning (RF)	Gastrointestinal and skin symptoms (GSS)
SF-36				
Physical functioning	−0.49**	−0.47**	−0.47**	−0.16 (*ns*)
Role-physical	−0.77**	−0.76**	−0.57**	−0.46**
Bodily pain	−0.56**	−0.52**	−0.43*	−0.45**
General health	−0.68**	−0.67**	−0.56**	−0.33*
Vitality	−0.63**	−0.64**	−0.45**	−0.34*
Social functioning	−0.30*	−0.30*	−0.23 (*ns*)	−0.12 (*ns*)
Role-emotional	−0.58**	−0.57**	−0.43*	−0.41*
Mental health	−0.51**	−0.51**	−0.34*	−0.34*
Physical component summary (PCS)	−0.57**	−0.55**	−0.52**	−0.23 (*ns*)
Mental component summary (MCS)	−0.52**	−0.49**	−0.40	−0.38
SGRQ				
Total	0.53**	0.52**	0.54**	0.09 (*ns*)
Symptoms	0.45*	0.45*	0.48*	0.03 (*ns*)
Activity	0.50**	0.49*	0.51**	0.13 (*ns*)
Impact	0.48*	0.48*	0.49*	0.06 (*ns*)
GHQ-12 *continuous*	0.74**	0.74**	0.50**	0.33*
EQ-5D				
VAS	−0.65**	−0.68**	−0.52**	−0.32**
Mobility	0.32**	0.36**	0.25*	0.06 (*ns*)
Self-care	0.24*	0.25*	0.20*	0.05 (*ns*)
Usual activity	0.59**	0.60**	0.51**	0.25*
Pain discomfort	0.53**	0.57**	0.36**	0.27*
Anxiety/depression	0.41**	0.43**	0.31**	0.21*
PGA				
PtGA	0.53**	0.56**	0.43**	0.27*
PhGA	0.17 (*ns*)	0.13 (*ns*)	0.25*	0.06 (*ns*)

CVID, Common variable immune deficiency; *EQ-5D*, EuroQol 5 dimensions; *GHQ-12*, General Health Questionnaire 12 Items; *ns*, not statistically significant; *PGA*, physician (PhGA)/patients (PtGA) global assessment; *QoL*, quality of life; *SF-36*, Short Form 36 questionnaire; *SGRQ*, Saint George Respiratory Questionnaire; *VAS*, visual analog scale.
*$P < .01$.
**$P < .001$.

self-reporting answers graded 3 ("often") and 4 ("always") to each item is shown in Table IV. The highest frequencies (≥25%) were observed for symptoms such as cough, asthenia, joint pain, and diarrhea, and for problems related to short- and long-term planning of their activities. The lowest frequencies (≤10%) were reported for problems related to immunoglobulin treatment and to the embarrassment to other patients, relatives, or unfamiliar persons due to different aspects of CVID.

DISCUSSION

Personalized care planning used in the management of chronic conditions should take advantages of discussions between patients and clinicians to identify critical issues related to the patient's illness. QoL is an important and established health care outcome depicting the impact of illness and treatment on the patient's personal experience. Clarity in understanding aberrations in QoL, and the specific factors of the disease that drive it, will contribute to empowering health care providers to target improvements for their patients.

Questionnaires such as the SF-36 have been designed for the evaluation of the health status in the general population.[19,20] However, specific and disease-related measurements to assess the burden of disease in patients with PAD have not been standardized nor validated as they have been in many other medical conditions. Several disease-specific questionnaires may have some utility in patients with PAD given the clinical spectrum and include the SGRQ,[21] the Inflammatory Bowel Disease Questionnaire,[11] and the Asthma Quality of Life Questionnaire.[12] A recent study in PAD used a generic tool (SF-36) in combination with a disease-specific tool (SGRQ) and demonstrated that much of the QoL impact in PAD was related to respiratory involvement, specifically the severity of airflow obstruction, respiratory exacerbation frequency, and dyspnea.[14] Although the information obtained from a general QoL instrument is of value in PAD, the advantages of using multiple tools simultaneously were demonstrated in 2 separate publications from our group. In the first study,[6] we used generic instruments (SF-36 and GHQ-12) to assess the health-related QoL. Mental health scales of SF-36 were less affected than physical scales and that being female, older, GHQ-positive, and alexithymic were major risk factors for poor health status. Approximately one-third of patients were at risk of anxiety and/or depression (two-thirds of females), and GHQ-positive patients had a greater burden of disease, suggesting the need for counseling. In a more recent study, we confirmed

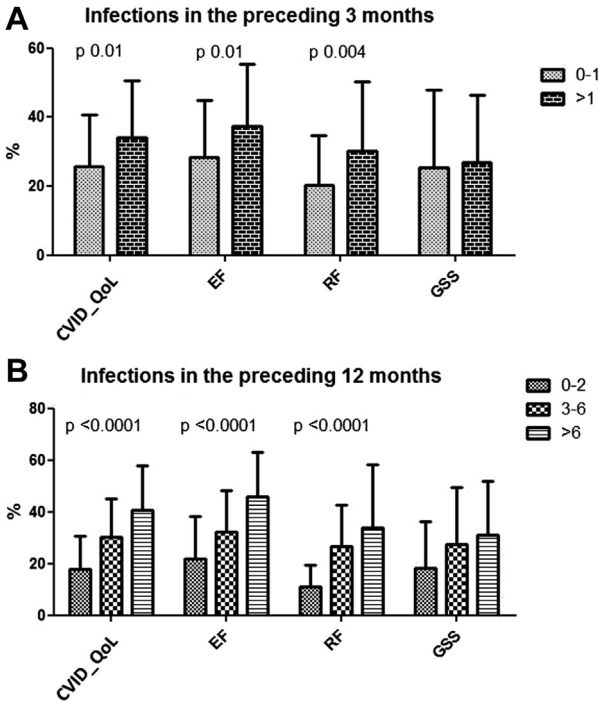

FIGURE 4. Number of infections and CVID_QoL scores. Patient groups were selected according to the number of self-reported episodes of infections in the 3 (**A**) and in the 12 months (**B**) preceding the study time. *P* values were calculated using the *t*-test and ANOVA. *CVID*, Common variable immune deficiency; *EF*, emotional functioning; *GSS*, gastrointestinal and skin symptoms; *QoL*, quality of life; *RF*, relational functioning.

TABLE IV. Questions referred as grade 3 "often" or grade 4 "always" by ≥ 25% (a) or ≤10% (b) by the entire CVID population

(a) Item no.	Question	Percent
6	I had a cough and/or phlegm	55
32	I felt tired	47
9	I had discomfort and/or pain in my joints	36
5	I had to give up making long-term plans	30
8	I was afraid that my health might worsen	29
2	I had to change my diet	26
4	I had diarrhea	25
13	I was concerned about my future	25
17	It was hard to do my usual work/studies	25
21	I was afraid of getting sick	25
(b) Item no.	**Question**	**Percent**
31	I felt troubled by relationships with other patients who have the same disease	0
27	I found it difficult to relate to people I spend time with	3
16	I was afraid I might make others sick with my infections	4
18	I was afraid of dying	5
26	I felt uncomfortable because of my skin problems (spots, redness, rashes, infections)	5
10	I needed help taking care of myself	6
29	I was embarrassed	6
12	I was afraid of adverse reactions to i mmunoglobulin therapy	7
19	I avoided leaving the house because of my cough	7
11	I was afraid I would run out of medication and/or immunoglobulin treatments	8
14	I avoided leaving my home because of diarrhea	8
20	I tended to isolate myself	8
23	My sexual activity was affected	9

CVID, Common variable immune deficiency.

the original data and showed that the combination of SF-36 with other questionnaires increased the possibility to identify correct measures for intervention and the potential to intervene to reduce disease burden.[10] Although the purpose of the general QoL instruments is in part to allow cross-comparison amongst diseases and distinct patient groups, the need to potentially administer multiple instruments to patients with PAD to most accurately define the QoL signal suggests the need for more specific measures for the PAD population.

With the aim of more accurately characterizing the PAD patient experience, we developed and validated a single disease-specific QoL tool for adults with CVID, the CVID_QoL questionnaire, potentially able to capture known disease-specific nuances that affect the burden of disease in CVID. Our objective for the CVID_QoL was to be able to assess the dimensions of the CVID experience, which may not be captured by existing instruments.

This study provides evidence of the reliability and constructs validity of the CVID_QoL instrument to assess health-related QoL in adult patients with CVID.

The CVID_QoL questionnaire takes approximately 10 to 15 minutes to complete and can be used to identify QoL issues that may not be addressed in generic QoL instruments or during routine patient encounters. The instrument had high internal consistency and high test-retest reliability.

The structure of the CVID_QoL and that of its dimensions were confirmed by factorial analysis: the final 32 items were organized into 3 dimensions: EF, RF, and GSS. Although respiratory symptoms were grouped within the relational and emotional dimensions, gastrointestinal and skin signs were considered as a separate dimension by factorial analysis. The relevance of the latter was confirmed by the clinical data showing a high impact of gastrointestinal diseases in CVID and a poor response to treatments.[28-30]

The highest impact within the CVID_QoL as self-reported by our patients was attributable to symptoms such as cough, asthenia, joint and muscle pain, diarrhea, and to problems related to short- and long-term planning of their activities. The lowest impact on reported health within the CVID_QoL was attributable to problems related to immunoglobulin treatment and to any embarrassment to other patients, relatives, or third parties. The low self-reported impact of Ig treatment in comparison with that of the disease manifestations themselves might explain the different results obtained by studies on QoL targeted to the analysis of treatment burden, without taking into account the overall disease load.[30-32]

Overall, correlations with the other questionnaires (SF-36, SGRQ, GHQ, and EQ-5D) were found. In particular, the emotional dimension (EF) was related to the comparable dimensions of SF-36, whereas the relational dimension (RF) was

related to physical dimensions of the SF-36. In contrast, the GSS dimension was related to the GHQ-12 score and to the dimension "activity/pain/discomfort" of the EQ-5D.

CVID_QoL and all its dimensions were also strongly related to overall burden and psychological well-being, as shown by the correlation with VAS EQ-5D and GHQ-12. The high correlation between CVID_QoL Global and its dimensions EF and RF with activity and impact scales of SGRQ demonstrated that the respiratory complications in CVID affected both the relational and the emotional areas.

All these data allowed us to conclude that CVID_QoL was able to identify broad characteristics relevant to patients with CVID and potentially capture signals specific to some but not all the general QoL instruments.

All dimensions correlated with PtGA and not with PhGA, and as we have already demonstrated in our previous work,[10] the correlation between PtGA and PhGA was low. This reinforces the concept that the use of a patient's reported outcome instrument is advisable in both research activities and clinical practice to truly define outcomes of relevance to patients with CVID.

Although the present study was focused on the cross-validation of the CVID_QoL, it was not designed to demonstrate superiority or improved utility compared with other tools. In this evaluation study, the entire cohort of patients attending our center were involved to minimize bias in the selection of the study population. Thus, it is difficult to presently compare our data with other studies in which stronger selection factors might have shaped the composition of the sample. In a recent paper[33] on perceived health in patients with primary immune deficiencies by the Immune Deficiency Foundation, factors driving perceived health status were educational level, age, acute and chronic diseases, hospitalization, limitation in the physical activities, "on demand" access to specialist care, the specialty of physician caring the patients, and regular Ig replacement therapy. We did not find any correlation between the CVID_QoL score with educational level and Ig treatment (although all of our patients were receiving Ig treatment) while we confirmed factors such as age and number of acute infections in patients affected by chronic illnesses.[34,35] Particularly, the number of infections in our study was self-reported but also cross-validated by clinical records and it represented an important factor for the higher CVID_QoL score.[14]

We recommend the widespread use of the CVID_QoL and its integration into research and clinical care, but appreciate that further investigation is required. It will be important to evaluate the performance of this instrument among larger numbers of patients across the continuum of age, disease activity, disease severity, duration, disability, and other PAD diagnoses to develop normative PAD data. It is also important to evaluate its performance in relevant subgroups and to demonstrate that the instrument is sufficiently responsive or sensitive to disease status changes over time. Similarly, the impact of treatment alterations on the CVID_QoL score is presently unclear, but we are hopeful that the additional focus on disease burden relevant to patients with CVID will allow for the highest resolution of measuring change. The additional studies of application of CVID_QoL in English as well as evaluation of its overall clinical utility, feasibility, and responsiveness to clinical status change are currently in progress. We are hopeful that this well-performing QoL tool can be used to supplement existing approaches to provide additional resolution in CVID regarding the perception that patients have of their well-being. The ability to better discern the impact of a clinical intervention or an early signal of exacerbation will hopefully help guide better clinical decisions and patient care.

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Questionario CVID_QoL

COGNOME : …… CODICE PAZIENTE ……
NOME: …… DATA ….……

Per favore, metta una crocetta sul ciascuna delle seguenti affermazioni che meglio descrive la sua condizione, considerando il suo stato di salute e la sua qualità di vita

A causa della mia malattia, negli ultimi tre mesi:

		Mai	Raramente	A volte	Spesso	Sempre
1	Mi sono sentito triste	☐	☐	☐	☐	☐
2	Ho dovuto modificare la mia alimentazione	☐	☐	☐	☐	☐
3	Ho provato rabbia	☐	☐	☐	☐	☐
4	Ho avuto diarrea	☐	☐	☐	☐	☐
5	Ho dovuto rinunciare a fare programmi a lungo termine	☐	☐	☐	☐	☐
6	Ho avuto tosse e/o catarro	☐	☐	☐	☐	☐
7	Non mi sono potuto occupare dei miei cari come avrei voluto	☐	☐	☐	☐	☐
8	Ho avuto paura che la mia salute potesse peggiorare	☐	☐	☐	☐	☐
9	Ho avuto fastidi e/o dolore alle articolazioni	☐	☐	☐	☐	☐
10	Ho avuto bisogno di aiuto nella cura della mia persona	☐	☐	☐	☐	☐
11	Ho avuto paura di restare senza medicine e/o immunoglobuline	☐	☐	☐	☐	☐
12	Ho avuto paura delle reazioni alla terapia con le immunoglobuline	☐	☐	☐	☐	☐
13	Sono stato preoccupato per la mia vita futura	☐	☐	☐	☐	☐
14	Ho evitato di uscire di casa a causa della diarrea	☐	☐	☐	☐	☐
15	Mi sono sentito meno autonomo del solito	☐	☐	☐	☐	☐
16	Ho avuto paura di contagiare gli altri con le mie infezioni	☐	☐	☐	☐	☐

1/2 Versione del 07/01/2015

FIGURE E1. The Italian version of the CVID_QoL questionnaire. *CVID*, Common variable immune deficiency; *QoL*, quality of life.

A causa della mia malattia, negli ultimi tre mesi:

		Mai	Raramente	A volte	Spesso	Sempre
17	Mi è stato difficile svolgere il mio lavoro abituale/ studiare	☐	☐	☐	☐	☐
18	Ho avuto paura di morire	☐	☐	☐	☐	☐
19	Ho evitato di uscire di casa a causa della tosse	☐	☐	☐	☐	☐
20	Ho avuto la tendenza ad isolarmi	☐	☐	☐	☐	☐
21	Ho avuto paura di ammalarmi	☐	☐	☐	☐	☐
22	Mi sono sentito fragile	☐	☐	☐	☐	☐
23	Sono stato condizionato nella mia attività sessuale	☐	☐	☐	☐	☐
24	Ho provato fastidio a causa della terapia con immunoglobuline	☐	☐	☐	☐	☐
25	È stato difficile svolgere le mie abituali attività del tempo libero	☐	☐	☐	☐	☐
26	Sono stato a disagio a causa dei problemi della mia pelle (macchie, rossore, infezioni)	☐	☐	☐	☐	☐
27	Ho avuto difficoltà a relazionarmi con le persone che frequento	☐	☐	☐	☐	☐
28	Mi sono sentito una persona malata	☐	☐	☐	☐	☐
29	Mi sono sentito in imbarazzo	☐	☐	☐	☐	☐
30	Ho avuto paura che gli altri mi potessero contagiare con le loro malattie	☐	☐	☐	☐	☐
31	Mi sono sentito turbato dalla relazione con pazienti che hanno la mia stessa malattia	☐	☐	☐	☐	☐
32	Mi sono sentito stanco	☐	☐	☐	☐	☐

Controlli di aver risposto **a tutte** le affermazioni.
Grazie della collaborazione.

2/2 Versione del 07/01/2015

FIGURE E1. (*CONTINUED*).

CVID_QoL Questionnaire

LAST NAME: ……
NAME: ……

PATIENT CODE……
DATE....……

Please place a check mark next to each of the following statements that best describes your condition, considering the state of your health and your quality of life

Because of my illness, in the last three months:

		Never	Rarely	Sometimes	Often	Always
1	I felt sad	☐	☐	☐	☐	☐
2	I had to change my diet	☐	☐	☐	☐	☐
3	I felt anger	☐	☐	☐	☐	☐
4	I had diarrhea	☐	☐	☐	☐	☐
5	I had to give up making long-term plans	☐	☐	☐	☐	☐
6	I had a cough and/or phlegm	☐	☐	☐	☐	☐
7	I could not take care of my loved ones as I would have liked to be able to	☐	☐	☐	☐	☐
8	I was afraid that my health might worsen	☐	☐	☐	☐	☐
9	I had discomfort and/or pain in my joints	☐	☐	☐	☐	☐
10	I needed help taking care of myself	☐	☐	☐	☐	☐
11	I was afraid I would run out of medication and /or immunoglobulin treatments	☐	☐	☐	☐	☐
12	I was afraid of adverse reactions to immunoglobulin therapy	☐	☐	☐	☐	☐
13	I was concerned about my future	☐	☐	☐	☐	☐
14	I avoided leaving my home because of diarrhea	☐	☐	☐	☐	☐
15	I felt less independent than usual	☐	☐	☐	☐	☐
16	I was afraid I might make others sick with my infections	☐	☐	☐	☐	☐

1/2 Version of 07/01/2015

FIGURE E2. The English version of the CVID_QoL questionnaire. *CVID*, Common variable immune deficiency; *QoL*, quality of life.

Because of my illness, in the last three months:

		Never	Rarely	Sometimes	Often	Always
17	It was hard to do my usual work / studies	☐	☐	☐	☐	☐
18	I was afraid of dying	☐	☐	☐	☐	☐
19	I avoided leaving the house because of my cough	☐	☐	☐	☐	☐
20	I tended to isolate myself	☐	☐	☐	☐	☐
21	I was afraid of getting sick	☐	☐	☐	☐	☐
22	I felt weak	☐	☐	☐	☐	☐
23	My sexual activity was affected	☐	☐	☐	☐	☐
24	Immunoglobulin therapy bothered me	☐	☐	☐	☐	☐
25	It was difficult to carry out my usual leisure activities	☐	☐	☐	☐	☐
26	I felt uncomfortable because of my skin problems (spots, redness, rashes, infections)	☐	☐	☐	☐	☐
27	I found it difficult to relate to people I spend time with	☐	☐	☐	☐	☐
28	I felt I was a sick person	☐	☐	☐	☐	☐
29	I was embarrassed	☐	☐	☐	☐	☐
30	I was afraid that I might get infected with other people's illnesses	☐	☐	☐	☐	☐
31	I felt troubled by relationships with other patients who have the same disease	☐	☐	☐	☐	☐
32	I felt tired	☐	☐	☐	☐	☐

Please check if you answered **all** the statements.
Thanks for your cooperation.

2/2 Version of 07/01/2015

FIGURE E2. (*CONTINUED*).