Longitudinal study on health-related quality of life in a cohort of 96 patients with common variable immune deficiencies

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Health-related quality of life (HRQoL) in common variable immunodeficiency diseases (CVID) was evaluated by different tools, which were mainly used to compare different schedules of immunoglobulins administration in cross-sectional or short-term longitudinal studies. We assessed the HRQoL and psychological status of CVID patients in a longitudinal study over a 6-year period by a generic, non-disease-specific instrument (SF-36), and by a General Health Questionnaire (GHQ-12) for the risk of depression/anxiety. At baseline, 96 patients were enrolled. After 1 year, a second assessment was performed on 92 patients and, after 6 years, a third assessment was performed on 66 patients. Eighteen patients died during the study time. HRQoL was low, with mental health scales less affected than physical scales. A decline in the score on SF-36 scales was observed between the first and the third assessment for the Physical Functioning, Body Pain, General Health, Social Functioning, and Role-Emotional scales. The General Health scale showed a lower score in these patients, when compared to patients with other chronic diseases. Approximately one-third of the patients were at risk of anxiety/depression at all observation times, a percentage that reached two thirds of the patients, considering only the group of females. Over the 6 years of the study, the health condition of 11/66 patients worsened, passing from “GHQ-negative” to “GHQ-positive”; their score on SF-36 scales also decreased. A decrement of one point in each of the Physical Functioning, Vitality, Social Functioning, and Mental Health SF-36 scales increased the risk of psychological distress. In a survival analysis with dichotomized variables, Physical Functioning scores <50 were associated with a relative risk (RR) of 4.4, whereas Social Functioning scores <37.5 were associated with a RR of 10.0. In our study, it was the clinical condition, as opposed to the different treatment strategies with immunoglobulins, which had a major role on the deterioration of HRQoL. Moreover, in a quality-of-life evaluation, disorders such as anxiety/depression should be assessed, as they yet often go unrecognized. Our results might be helpful in the interpretation of currently available data on quality of life in CVID patients.

Keywords: common variable immune deficiencies, health-related quality of life, SF-36, GHQ-12, immunoglobulins

INTRODUCTION

The health-related quality of life (HRQoL) is a multidimensional concept that encompasses measurements of physical, psychological, and social well-being and assesses the individual’s perception of the impact of illness on his/her life (1).

Common variable immunodeficiency diseases (CVIDs) represent a heterogeneous group of rare chronic disorders of the immune system (2). The prognosis can vary from benign to very complex conditions (3). There is substantial evidence that the standard replacement treatment with immunoglobulins prolongs survival, reduces morbidity, and exerts a positive effect on the patients’ HRQoL (4). Until now, different tools to evaluate HRQoL in CVID were used mainly to assess the patients’ outcome and satisfaction related to different treatment choices (i.e., intravenous-IVIG vs. subcutaneous-SCIG immunoglobulin routes of administration) (5, 6). However, HRQoL in CVID should be assessed in the frame of the wide spectrum of the severity of the disease, taking into consideration the long life course of the disease.

There are several critical reasons to evaluate the available data on HRQoL in CVID. The absence of a disease-specific questionnaire is a major limitation. Only observational or short-term longitudinal studies on small cohorts were performed. Differences in HRQoL were mainly evaluated to compare different treatment regimens and routes of immunoglobulins administration.
With such limitations in evaluating quality of life in CVID, both ourselves and others (7–9) have used generic, non-disease-specific instruments, such as the Health Status Questionnaire (Medical Outcome Study 36-Items Short Form, SF-36) and the General Health Questionnaire (GHQ-12 Items) for the psychological assessment. All the studies agreed that CVID patients have a poor quality of life, especially in the physical domain, suffer a lot, and are at risk of psychological distress.

Because of the long lifetime of the disease, it is possible to speculate that quality of life in a population affected by a clinical and immunological heterogeneous disease may vary depending on age, treatment, clinical conditions, associated diseases, personal attitude, etc. Thus, it is evident that studies about the HRQoL outcome in CVID should be extended from a simple assessment to multimodal and longitudinal assessments and should include the patients’ reported outcome measures.

The aim of this study was to assess the HRQoL and psychological status of patients with CVID over a 6-year period, using SF-36 and GHQ-12 questionnaires. Moreover, we investigated whether the psychological problems of patients, such as risk of depression/anxiety, could be associated with their health status.

MATERIALS AND METHODS

STUDY DESIGN

For this observational, longitudinal, cohort study (Figure 1), performed in a day hospital setting, patients’ participation was obtained after signing an informed consent. The study was conducted in the period 2008–2013. One hundred twelve CVID patients were informed and considered eligible for the study. At basal time (T0), 96 patients were enrolled and 16 patients refused to participate. After 1 year, at the second assessment (T1) 92 out of 96 patients were evaluated (between T0 and T1 two patients died and two patients refused to continue the study). After 6 years, 66 out of 92 patients were available for the third assessment (T2). Between T1 and T2, 12 patients refused to participate and 16 patients died in the 5-year period. At the end of the study, data for the 66 patients were considered, taking into account all three observations. At T0, T1, and T2, patients were asked to fill in questionnaires concerning their health status and the possible presence of risk for depression and/or anxiety. The severity of disease judged by the physician (Physician Global Assessment, PhGA) and by the patient (Patient’s Global Assessment, PtGA) was recorded. The study protocol was approved by the Ethical Board of the Sapienza, University of Rome.

PATIENTS

We enrolled 112 patients with CVIDs attending our Reference Center for Primary Immune Deficiencies. Patients were diagnosed according to the ESID/PAGID criteria for CVIDs (10), based on IgG <500 mg/dL, IgA 2 SD below age-specific reference range, age onset >4 years, poor response to vaccines, and exclusion of other causes of hypogammaglobulinemia. No genetic causes of CVID were identified in this cohort. A detailed set of data was available, since all patients with a diagnosis of CVID have been regularly followed up in our center according to the Italian guidelines (www.aieop.org); their clinical and immunological data have been collected regularly in a national database, once a year. The dataset included age, date of CVID diagnosis, immunological data, including lymphocyte subsets and serum IgG, IgA, and IgM levels determined every 3 months, clinical manifestations, route, doses, and intervals of Ig replacement, and occurrence of adverse reactions. Route, dosage, and interval of Ig replacement were recorded once a month. At T0, 84 patients were on replacement therapy with IVIG and 12 with SCIG. Between T0 and T2, 6/66 patients shifted from IVIG to SCIG. High-resolution chest computerized tomography (HRCT) scans was performed once in every 4 years in all patients according to national guidelines. All patients have been on IVIG or SCIG replacement for at least 5 years.

QUESTIONNAIRES

We used validated tools: SF-36, GHQ-12, and PGA questionnaires. SF-36

Despite the fact that it was designed as a generic health status indicator for use in population surveys and health policy evaluation studies, the SF-36 can also be used as an outcome measure (11, 12). The SF-36 includes 36 items in a Likert-type or forced-choice
format, intended for measuring the following eight dimensions: physical functioning (PF, limitations in performing physical activities such as bathing or dressing), role-physical (RP, limitations in work and other daily activities as a consequence of physical health), bodily pain (BP, how severe and limiting pain is), general health (GH, how general personal health is perceived by the patient), vitality (VT, feeling tired and worn out vs. feeling energetic), social functioning (SF, interference with regular social activities because of physical or emotional problems), role-emotional (RE, limitations in work and other daily activities as a consequence of emotional problems), and mental health (MH, feeling nervous and depressed vs. peaceful, happy, and calm). Scores for each domain ranged from 0 to 100, with higher scores indicating better health. Two additional summary measures, the physical component summary (PCS) and mental component scores (MCS), cross-culturally validated in the framework of the International Quality of Life Assessment project for the Italian version of the SF-36, were also obtained.

GHQ-12
The GHQ-12 is a self-administered, 12-item questionnaire, designed to measure psychological distress and to detect current non-psychotic, psychiatric disorders, such as depression and anxiety (13, 14). Answers are given on a 4-point scale; for instance, the item “in the last weeks, did you feel under strain?” allows for the following answers: “no,” “not more than usual,” “more than usual,” and “much more than usual.” When scored with the binary method (0–0–1–1), the GHQ-12 can be used as a screening tool to detect minor non-psychotic, psychiatric disorders, yielding final scores that range from 0 to 12. Operationally, patients scoring 4 or more were considered as “GHQ-positive” (GHQ+).

PGA
For each patient, an overall clinical severity evaluation of the disease was given by the provider and by the patient him/herself. The PhGA and the PtGA consisted of the following questions respectively: “In your opinion, compared to other patients with the same condition, how severe is the disease of patient X?” and “In your experience, how severe is your disease?” Answers were given on a 5-point scale: “very mild,” “mild,” “moderate,” “severe,” and “very severe.” For the purpose of statistical analysis, “very mild”/“mild” were considered as low severity and “severe”/“very severe” as high severity, and were grouped. The same physician at T0, T1, and T2 recorded her evaluation at the end of the visit. Patients recorded his/her evaluation after the completion of the questionnaires.

STATISTICS
In the first part, for descriptive analyses and comparisons among groups, we used t-test for independent samples and ANOVA for the comparison of mean values, due to the samples’ size. Chi-squared test was also used for the comparison of percentages. For the 66 patients present in each observation, paired tests were used. In the second part, we performed a logistic regression analysis to assess the independent role of SF-36 scales on GHQ-12 deterioration over time. In the last part, in order to investigate factors predicting mortality, survival analysis was performed, both through Kaplan–Meier curves and Cox regression analysis. All analyses were performed using the Stata version 11 (Stata Corp, College Station, TX, USA).

RESULTS
The study design flow chart on CVID patients enrolled in the cohort study is shown in Figure 1. One hundred twelve patients were enrolled; 96 patients accepted to participate in the study [M/F: 50/46; mean age: 48.2 ± 17.0 years old (range 14–85); mean time of disease since diagnosis: 10.7 years (range 5–36)]; 92 patients [M/F: 47/45; mean age: 49 ± 4.9 years old (range 15–86)] completed the second assessment. Sixty-six patients [M/F: 32/34; mean age: 50 ± 5.7 years old (range 20–76)] completed the T0, T1, and T2 assessments. Thirty patients refused to participate (16 at T0, 2 at T1, and 12 at T2). Eighteen patients [M/F: 9/9; mean age: 62.9 ± 14.7 years old (range 39–88)] died in the 6-year period. Causes of death were: gastrointestinal cancer (5 patients), lymphoproliferative diseases (5 patients), chronic lung disease (CLD) (2 patients), cirrhosis (1 patient), and granulomatosis (5 patients).

DESCRRIPTIVE ANALYSES
Patients’ characteristics at baseline and comparison between SF-36 in CVID and in other chronic diseases
At baseline (T0), the characteristics of patients were those reported in our study published in 2012 (7). A summary of our previous data on HRQoL is reported in Table 1. Being female, older, and affected by CLD and chronic diarrhea proved to be major risk factors leading to a poor quality of life. The basal mean scores for SF-36 scales were also compared to those reported (12) on patients affected by other chronic diseases (Table 2). HRQoL was lower than that reported in generally healthy population, with mental health scales less affected than physical scales. In CVID, better scores for PF, BP, VT, SF, RE, and MH scales were observed, while RP and GH scales showed a lower score in comparison to patients with all other disease entities, with the exception of patients affected by heart failures who showed the lowest scores. The different age range of patients in each group (older in cancer, younger in CVID) has a significant effect on profiles of SF-36 average scores. Therefore, one must be cautious in the interpretation of differences in SF-36 scores between pathologies: they cannot be entirely attributed to the “pure” effect of the disease. This consideration is even more valid in the longitudinal study.

Longitudinal variation of SF-36
Longitudinal variations in SF-36 scores were observed over the whole sample, as well as over the subsample of 66 patients attending all three sequential assessments. The scores observed considering the SF-36 mean values in the 66 patients, who were followed at all three points of observation times, are shown in Figure 2. Differences in the scores of SF-36 scales between T0 and T2 are statistically significant for the following scales: PF (p = 0.03), BP (p = 0.05), GH (p = 0.02), SF (p = 0.002), and RE (p = 0.03). However, we should consider the age dependence of all scales, especially because patients at T2 were 6 years older than at T0. Moreover, we found no differences in HRQoL scales between patients on replacement with IVIG and SCIG.
Table 1 | SF-36 mean values (SD) and clinical characteristics of CVID patients.

| n   | PF   | RP   | BP   | GH   | VT   | SF   | RE   | MH   | PCS  | MCS  |
|-----|------|------|------|------|------|------|------|------|------|------|
| All | 96   | 72 (25) | 47 (42) | 67 (26) | 39 (24) | 55 (22) | 69 (22) | 68 (40) | 66 (20) | 40 (12) | 43 (12) |
| Gender |     |      |      |      |      |      |      |      |      |      |
| Male | 50   | 78 (24) | 59 (41) | 73 (25) | 44 (27) | 62 (20) | 72 (23) | 74 (38) | 69 (20) | 43 (12) | 45 (12) |
| Female | 46   | 66 (25) | 34 (40) | 60 (26) | 34 (20) | 47 (21) | 66 (21) | 62 (42) | 63 (19) | 36 (11) | 42 (12) |
| Age |     |      |      |      |      |      |      |      |      |      |
| <50 years | 52   | 84 (19) | 56 (42) | 74 (26) | 43 (27) | 59 (21) | 69 (24) | 79 (33) | 68 (19) | 44 (12) | 44 (12) |
| ≥50 years | 44   | 58 (25) | 34 (40) | 60 (26) | 35 (21) | 51 (22) | 70 (20) | 55 (43) | 64 (21) | 34 (11) | 43 (13) |
| Duration of disease |     |      |      |      |      |      |      |      |      |      |
| ≤8 years | 47   | 73 (28) | 49 (42) | 69 (28) | 42 (23) | 55 (20) | 69 (24) | 72 (38) | 63 (20) | 41 (13) | 43 (13) |
| >8 years | 46   | 71 (23) | 44 (42) | 65 (26) | 37 (27) | 56 (24) | 69 (21) | 64 (42) | 68 (20) | 39 (12) | 44 (12) |
| Co-morbidities |     |      |      |      |      |      |      |      |      |
| CLD | 62   | 70 (25) | 41 (41) | 63 (26) | 37 (23) | 54 (23) | 65 (23) | 60 (41) | 63 (21) | 38 (12) | 41 (13) |
| Sinusitis | 48   | 73 (25) | 44 (43) | 66 (28) | 36 (23) | 54 (22) | 68 (22) | 65 (42) | 65 (22) | 39 (12) | 42 (13) |
| Diarrhea | 42   | 65 (26) | 37 (40) | 60 (29) | 34 (24) | 51 (23) | 65 (24) | 54 (41) | 63 (22) | 36 (12) | 41 (13) |

SF-36 scales: PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; PCS, physical component summary; MCS, mental component summary; CLD, chronic lung disease; CVID, common variable immunodeficiency.

Bold – p < 0.05.

Totals may vary because of missing values.

Table 2 | Mean values of SF-36 scales for CVID patients compared with healthy subjects and with patients with different chronic diseases in Italy.

| N   | PF   | RP   | BP   | GH   | VT   | SF   | RE   | MH   |
|-----|------|------|------|------|------|------|------|------|
| Healthy subjects | 608   | 973 | 94.3 | 89.2 | 80.2 | 72.2 | 86.4 | 88.0 | 75.8 |
| Diabetes | 98   | 62.9 | 59.7 | 59.8 | 43.6 | 476 | 66.9 | 576 | 53.4 |
| Heart failure | 129 | 49.5 | 43.1 | 476 | 35.4 | 38.3 | 54.8 | 46.3 | 46.6 |
| Cancer | 34   | 60.6 | 62.4 | 570 | 44.9 | 48.3 | 64.1 | 58.6 | 49.9 |
| Chronic obstructive pulmonary disease | 188 | 58.7 | 49.5 | 52.0 | 41.5 | 45.8 | 62.6 | 55.8 | 53.5 |
| Mental disorders | 180 | 65.4 | 49.5 | 51.9 | 44.7 | 40.9 | 55.0 | 43.7 | 42.0 |
| CVID | 96   | 72.4 | 47.3 | 67.2 | 39.3 | 55.2 | 69.5 | 68.3 | 66.3 |

SF-36 Scales: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), Mental Health (MH). SF-36 values for Italian diseases (12).

GHQ assessment and PtGA/PhGA

GHQ-12 assessment showed that more than 35% of the patients were at risk of anxiety and depression (GHQ-positive) at all observation times (Table 3). This percentage was increased to about 70% in females. The disease severity perception graded by patients and by physicians at the three points of observation is reported in Table 3. Differences between the perception of patients and physicians were more evident at T2, with higher percentage of low severity grade reported by physicians. As expected, PtGA was greater in GHQ-positive patients. Twenty-five percent of GHQ-positive patients considered their disease severity as high.

The 15 patients who were permanently GHQ-positive at all observations had constantly low mean values of scores on SF-36 scales. Patients with a highly severe perception of the disease (PtGA) and patients who were judged as seriously affected by the physicians (PhGA) reported a lower health status with respect to the others.

GENERAL HEALTH QUESTIONNAIRE DATA AND VARIATIONS OF MEAN VALUES IN SPECIFIC SF-36 SCALES

To analyze the relationship between SF-36 and GHQ-12 data, variation in GHQ status between T0 and T2 were coded as 1 when GHQ passed from 0 to 1 (GHQ-worsened) and as 0 in all other instances (GHQ-stable/improved). Changes in SF-36 scales were recorded as absolute differences between values at T0 at T2. Average variation in SF-36 scores was then compared between the group of GHQ-worsened and GHQ-stable/improved. The SF-36 scales showing variations significantly different in the two groups (GHQ-worsened and GHQ-stable/improved) were selected.

Over the 6-year observational period, the general health condition of 11/66 patients worsened, passing from “GHQ-negative” to “GHQ-positive” status, i.e., showing symptoms of psychological distress.

These patients also registered a negative score variation on SF-36 scales: Physical Functioning, Vitality, Social Functioning, and Mental Health. In a logistic regression, controlled for age...
and gender, we noticed that a decrement of 1 point in each of the four mentioned scales increases the risk of developing anxiety/depression from 3 to 5% (Table 4). Thus, the GHQ-12 and SF-36 deteriorations were strictly linked. To convey an idea of the magnitude of the effect, we considered the cumulative observed variation of the Physical Functioning scale (PF) over the follow-up period: 10 points. The odds ratio of 1.05 means that a patient affected by the average negative variation of PF has an increased risk of 5% per year of psychological distress. Also VT, SF, and MH subscales were strongly influenced by GHQ status (Figure 3).

Table 3 | Gender, GHQ status, and disease severity reported by patients and by physicians at each assessment (numbers and percentages).

|                  | All  | All  | All  |
|------------------|------|------|------|
|                  | n.96 (T0) (%) | n.92 (T1) (%) | n.66 (T2) (%) |
| Sex              |      |      |      |
| Males            | 52   | 51   | 52   |
| Females          | 48   | 49   | 48   |
| GHQ+             |      |      |      |
| Males            | 28   | 23   | 33   |
| Females          | 72   | 77   | 67   |
| PrGA             |      |      |      |
| Low              | 27   | 17   | 38   |
| Moderate         | 49   | 49   | 40   |
| High             | 24   | 33   | 22   |
| PhGA             |      |      |      |
| Low              | 17   | 16   | 47   |
| Moderate         | 50   | 51   | 39   |
| High             | 33   | 33   | 14   |

PrGA, Patient Global Assessment; PhGA, Physician Global Assessment. GHQ, General Health Questionnaire; GHQ+, GHQ-positive “cases” or GHQ ≥4.

Table 4 | Odd ratio (OR) and p-values for SF-36 scales for “changes” in GHQ-12 status (from negative to positive).

| SF-36 scale | OR     | p-value |
|-------------|--------|---------|
| PF          | 1.05   | 0.012   |
| VT          | 1.04   | 0.008   |
| SF          | 1.03   | 0.024   |
| MH          | 1.04   | 0.03    |

IMMUNOLOGICAL DATA AND HRQoL

In CVID, we have previously identified (15) a severe clinical phenotype, characterized by low IgA level (<7 mg/dL) and low switched memory B cells, confirming previous observations showing that the loss of function of memory B cells seems to represent the major cause of CVID-associated clinical conditions (16). Moreover, clinical improvement of CVID was observed in patients receiving high Ig dosages, >600 mg/kg/months (17, 18). These dosages might allow to keep IgG trough levels >600–800 mg/dL. We then grouped our CVID cohort on the basis of three defined parameters: IgA >7 mg/dL, IgG trough levels >600 mg/dL, switched memory >2%. At T0, 67% of the patients had IgA levels <7; 50% had switched memory B cells <2%; 61% had IgG levels >600 mg/dL (a percentage ranging from 14 to 26 has missing information on these parameters).

The analysis of the mean values on SF-36 scales in patients with or without each defined parameter showed no statistically significant differences among groups.

LOW HRQoL WAS PREDICTIVE OF MORTALITY

Patients’ mortality during the follow-up was registered with exact date of death. According to this outcome, patients at T0 were
divided into two groups: survivors vs. deceased. Cox Survival analysis was performed, introducing as covariates the SF-36 scales that showed marked differences between survivors and deceased at T0. Age and gender were also included in the analysis in order to estimate the role of HRQoL in predicting mortality, as adjusted by these two variables. For the SF-36 scales independently predictive of mortality, we operated a dichotomization of values, indicating “at-risk” and “not at-risk” patients. The cut-off values were selected observationally based on points of disruption in the trend of number of death over SF-36 scores. For SF-36 scales predictive of mortality, we graphed the two groups (“at-risk” and “not-at-risk”) with Kaplan–Meier survival curves, whose significance was verified by Log-rank test. A new Cox survival analysis with SF-36 scales dichotomized was produced, in order to assess the specific risk of death for the patients that scored under the cut-off at T0. The most evident difference between the two groups (Table 5) is, not surprisingly, in terms of age: survivors are significantly younger than deceased patients. However, score values of Physical and Social Functioning as well as Role Emotional at T0 seem to be remarkably reduced for patients that died during the study time. This result was partially confirmed when adjusted by age: except for the Role Emotional, which has no age-independent effect on mortality, both Physical and Social Functioning score values maintain their significant predictive power.

The relative risk (RR) of death associated with PF and SF scales is 0.98 and 0.97, respectively, meaning that each point increase in Physical and Social Functioning scores, independently of age, reduced the risk of death by 2% and 3%. The two predictive scales (PF and SF) were then dichotomized based on the observed point of disruption in the trend of number of deaths per different scores of PF and SF. More specifically, a cut-off value of 50 was selected for PF and a value of 37.5 for SF. People with values higher than the cut-off were classified as “not-at-risk,” compared to the “at-risk” below the cut-off. In a survival analysis with these dichotomized variables, PF scores <50 were associated with a RR of 4.4 (CI: 1.7–11.8, \(p < 0.03\)) and SF scores <37.5 determined a RR of 10.0 (CI: 2.6–37.9, \(p < 0.001\)). In other words, all other variables being equal, patients with scores below the cut-off in Physical Functioning have 4.4 times the risk of dying than patients with higher scores; the same risk is 10 times higher for patients under the cut-off in Social Functioning. Figures 4A,B compare survival rates over the follow-up period, between “at-risk” and “not at-risk” patients as classified by T0 for PF/SF scores. The difference is extremely significant with the “at-risk” group survival curve always below the “not-at-risk” curve (Log-rank test <0.0001). The median value was approached in both the “at-risk” groups, meaning that half of the patients have died at 48 months (SF) and 60 months (PF), whereas, the percentage of death in the “not-at-risk” groups is lower than 25% at the end of the observation period (72 months).
**Table 5 | Characteristics of survival and deceased patients.**

| Characteristics                      | All patients, $N = 96$ | Survived patients, $N = 78$ | Deceased patients, $N = 18$ | $p$-Value |
|--------------------------------------|------------------------|-----------------------------|-----------------------------|-----------|
| **SF-36 scores, mean (SD)**          |                        |                             |                             |           |
| PCS                                  | 39.8 (12.4)            | 40.8 (12.5)                 | 35.5 (10.9)                 | 0.06      |
| MCS                                  | 43.4 (12.2)            | 44.0 (12.1)                 | 41.0 (12.9)                 | 0.18      |
| Physical Functioning                 | 72.4 (25.4)            | 76.9 (23.4)                 | 53.8 (25.8)                 | 0.001     |
| Role-Physical                        | 47.3 (42.3)            | 50.3 (42.4)                 | 34.7 (40.3)                 | 0.08      |
| Body Pain                            | 67.1 (26.5)            | 67.5 (26.9)                 | 65.9 (25.9)                 | 0.41      |
| General Health                       | 39.3 (24.5)            | 40.1 (25.3)                 | 36.0 (21.2)                 | 0.27      |
| Vitality                             | 55.2 (21.8)            | 56.8 (21.1)                 | 48.6 (23.8)                 | 0.08      |
| Social Functioning                   | 69.5 (22.2)            | 71.5 (21.6)                 | 61.1 (23.4)                 | 0.04      |
| Role-Emotional                       | 68.3 (39.8)            | 73.1 (37.9)                 | 48.1 (44.8)                 | 0.0008    |
| Mental Health                        | 66.3 (19.9)            | 67.6 (19.1)                 | 60.7 (22.8)                 | 0.09      |
| Age, mean years (SD)                 | 48.2 (170)             | 44.8 (15.7)                 | 62.9 (14.7)                 | 0.0001    |
| Gender, men%                         | 52.2                   | 52.6                        | 50.0                        | 0.84      |
| GHQ, cases%                          | 26.6                   | 28.6                        | 27.7                        | 0.36      |
| IgA, > 7 mg/dL%                      | 32.9                   | 33.3                        | 30.0                        | 0.83      |
| IgG, > 600 mg/dL%                    | 61.0                   | 63.9                        | 40.0                        | 0.5       |
| SW mem, >2%                          | 50.0                   | 50.8                        | 44.4                        | 0.72      |

**DISCUSSION**

Patient reported outcome measures in clinical practice, in particular, those evaluating HRQoL (19), have been proposed as a means of facilitating doctor–patient communication, uncovering patients’ problems, as well as monitoring disease or treatment, and as a screening for functional problems (20, 21). In a previous study on HRQoL performed in our cohort of CVID patients, we showed (7) a low HRQoL in particular in physical domains: the Role-Physical and the General Health scales of the SF-36 questionnaire. Moreover, we showed that being female, older, and GHQ-positive proved to be major risk factors associated with a poor health status. Here, we extended the study time over a 6-year period. To our knowledge, this is the first longitudinal assessment of HRQoL in adult CVID patients. We confirmed that HRQoL was lower than that reported in generally healthy population with mental health scales less affected than physical scales. Moreover, Physical Role and General Health scales showed the worse scores at all observational times and were lower than those reported in patients with other chronic disease entities (12), with the exception of patients affected by heart failures. Our data on HRQoL confirmed the data reported 10 years ago in the first multidimensional assessment on HRQoL in adult CVID patients (23) and more recently in a survey run by IPOPI (4). However, SF-36 scales showed less severe defects than those previously reported, possibly because of the over-representation of females in both studies. All studies recognized limitations in work and other daily activities as a result of declined physical health and general health. HRQoL measures ensure that treatment and evaluations are focused on the patient rather than on the disease, and may be used as a way of capturing the personal and social context of patients and linking it to the classical clinical view of the disease. However, while HRQoL measures are now quite commonly included in the protocols of randomized, controlled clinical trials and other clinical studies, their use in routine clinical practice is still quite limited; they were never used in combination with other questionnaires, limiting the
However, a major limitation in the assessment of HRQoL in CVID is the absence of a disease-specific questionnaire available to monitor quality of life in many other diseases. We are now developing and validating a CVID-disease-specific questionnaire on HRQoL necessary to complement evidence-based guidelines and policies.

**AUTHOR CONTRIBUTIONS**

Stefano Tabolli: designed research, analyzed data, and wrote the manuscript; Patrizia Giannantoni: performed the statistical analysis; Federica Pulvirenti: performed research, collected, and analyzed data; Fabiola La Marra: performed research, collected, and analyzed data; Guido Granata: performed research, collected, and analyzed data; Cinzia Milito: performed research, collected, and analyzed data; Isabella Quinti: designed research, analyzed data, and wrote the manuscript.

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