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RESEARCH ARTICLE

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Validity and Reliability of the Turkish Version of the Quality-of-Life Questionnaire in Adult Patients with Common Variable Immune Deficiency

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ABSTRACT

Objective: Common variable immunodeficiency (CVID) can affect the quality of life (QoL), which can be better assessed with validated scales. Our goal was to validate the Turkish version of the Italian CVID-QoL questionnaire..

Materials and Methods: International recommendations for the cultural adaptation and translation process of the original scale were followed. CVID patients completed the Turkish CVID-QoL questionnaire between October 2019 and January 2020. The Short Form Health Survey (SF-36) was used as a comparative questionnaire. Reliability, reproducibility, factor analysis, content validity, convergent validity, and discriminant validity were analyzed.

Results: Fifty CVID patients were included in the study. 64% of the patients (n=32) were male, the mean age of the patients was 36.68 ± 13.2 years, and the median duration of disease was 52.5 months. The instrument had good internal consistency in 50 patients [Cronbach's alpha: 0.92, emotional functioning (EF): 0.91, relational functioning (RF): 0.77]. Twenty-six patients answered the survey questions again within 14-21 days. Reproducibility was very high; QoL global, intraclass correlation coefficient (ICC)=0.80 (95% CI 0.56-0.91); EF, ICC=0.78 (95% CI 0.51-0.90); RF, ICC=0.82 (95% CI 0.59-0.92); Gastrointestinal and skin symptoms (GSS), ICC=0.89 (95% CI 0.76-0.95); ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$). QoL global, EF and RF scores showed good convergent validity with the similar subscales of SF-36. The number of infections within the last 3 months had a significant impact on QoL global ($p=0.038$), EF ($p=0.045$) and RF ($p=0.028$).

Conclusion: The Turkish version of the CVID QoL scale has appropriate validity and reliability among Turkish patients with CVID.

Keywords: Common variable immune deficiency, linguistic validation, quality of life, scale validation

INTRODUCTION

Common variable immunodeficiency (CVID) is one of the most frequent and commonly diagnosed symptomatic inborn errors of immunity in adults (1-3). CVID is characterized by various clinical conditions such as severe infections, malignancy, and granulomatous and autoimmune disorders (1). Immunoglobulin (Ig) replacement is the main treatment for preventing recurrent infections, but it is less effective on other CVID-associated complications (4,5).

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Patient-focused assessment methods have become increasingly important in the follow-up of patients with chronic diseases (6). CVID is a rare disease that exerts diverse psychological and social effects on society, individuals, and healthcare providers. However, there are only a few studies analyzing its psychosocial aspects, resulting in a significant knowledge gap (7,8). In recent years, considerable progress in early diagnosis, increased awareness and Ig replacement therapy has led to a significantly extended life expectancy for patients with primary antibody deficiencies (9).

Quality of life (QoL) assessment is a comprehensive concept important for evaluating the impact of disease, treatment, and symptoms on an individual's life (10). QoL is a crucial health outcome, representing the ultimate goal of all health interventions and the use of valid and reliable measurements is essential for providing evidence-based healthcare (11).

The measurement of health-related quality of life (HRQoL) in primary immunodeficiency has emerged relatively recently from efforts to document the outcome of therapeutic intervention and need to obtain information about patients' well-being as well as objective findings visible to physicians (12). On the other hand, manifestations of CVID resemble those of more common diseases and have been frequently investigated. However, there is insufficient knowledge about the effects of Ig replacement therapy on patients. Thus, the development and validation of a disease-specific HR-QoL survey tool and researchers' understanding of the quality of life of CVID patients are necessary.

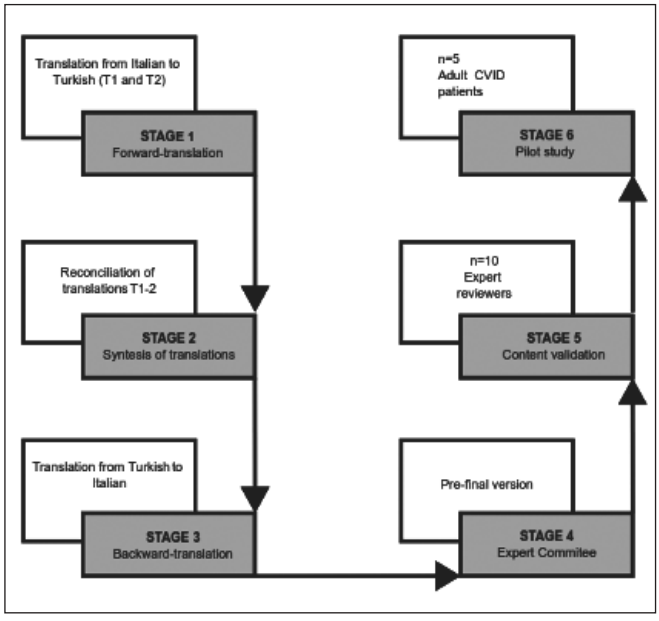

Figure 1. Flowchart of the stages of cross-cultural adaptation and content validation of CVID QoL.

T1-T2: *first and second translations from Italian to Turkish,* ***CVID:*** *common variable immune deficiency.*

In previous studies, generic health status QoL scales were used such as Short form (SF-36, SF-12) and General Health Questionnaire (GHQ-12) in adult CVID population (12-14). Quinti et al. developed the CVID-specific QoL questionnaire in 2015 (9) and it has been used in scientific studies in Norway and Italy (15,16).

The aim of this study was to translate this Italian CVID-QoL scale into Turkish and investigate the validity and usefulness of the CVID-QoL questionnaire. Additionally, we aimed to determine the impact of CVID on quality of life for use with adult CVID patients by healthcare professionals and researchers.

MATERIALS and METHODS

Instrument Translation of CVID-QoL

To achieve linguistic equivalence with the original questionnaire, we followed a systematic methodology known as standardized linguistic validation based on international consensus (17,18). Two separate forward translations from Italian to Turkish were conducted, and they were reconciled into a single version. Subsequently, the backward translation of the reconciled version was compared with the original questionnaire by the expert committee. This process resulted in the creation of the pre-final Turkish version of the questionnaire (Figure 1). In this pre-final version, the content validity index was determined for each item by ten experts by using the options 1= "not suitable", 2= "partially suitable, applicable by modification", 3= "the item available as it is". Following this step, CVID-QoL-TR questionnaire was individually administered to five eligible patients as part of a pilot study. During this phase, we collected their feedback on the understandability of all 32 items (Table I) and solicited suggestions for changes. Finally, after incorporating their feedback, the last version was approved.

Patient Selection

This methodological study was conducted at İstanbul University, Faculty of Medicine, Adult Immunology and

Allergy Clinic. To be eligible for inclusion, participants had to meet all of the following criteria: age greater than 18 years, diagnosis of CVID for more than 6 months, and currently receiving intravenous or subcutaneous immunoglobulin replacement therapy. The diagnosis of CVID was made according to the ESID criteria (19). Exclusion criteria included inability or unwillingness to provide informed consent and significant medical or psychiatric illness were the exclusion criteria.

Procedures

Demographic and clinical characteristics were recorded: including age, gender, education level, number of infections experienced within the 3 and 12 months before participation (self-reported), disease duration, Ig levels at the time of diagnosis, the last IgG trough levels, current body mass index, route of Ig administration.

We used the SF-36 as a comparative questionnaire.

Patients were asked "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 patient general assessment (PtGA) was completed before meeting the physician as were other two questionnaires. At the end of the visit, physicians also evaluated the disease severity of each patient with physician general assessment (PhGA) with the same 5-scale.

Factor analyses was conducted to evaluate both QoL scores and percentages to ensure the accuracy of the analyses.

The CVID-QoL-TR was applied to the participants 14-21 days after the first evaluation to assess the reproducibility.

The institutional review board and the Ethics Committee of İstanbul University, Faculty of Medicine approved the study (149, 2019/ 1453) and informed consent was obtained from all study participants.

Statistical Analyses

Statistical data analysis was performed using SPSS.21 version. Normality analysis showed that all continuous variables for all groups did not confirm normal distribution. Categorical variables were summarized as frequencies and percentages; continuous variables were given by using means and standard deviations when normally distributed, median (min-max) when abnormally distributed. Two measures of reliability were included: internal consistency and test–retest reliability. Internal consistency was tested using Cronbach's alpha for the patient group. Test–retest reliability was carried out using Intraclass Correlation (ICC). Construct validity was assessed by estimating Spearman's correlation coefficients between the subscales of the CVID-QoL-TR and the items of the SF-36. Additionally, Mann-Whitney-U test and Kruskal- Wallis test was conducted to evaluate the discriminant validity of the tool.

Table I: CVID QoL dimensions identified by factor analysis of index study.

CVID QoL	EF	1 Sadness 3 Anger 5 Difficulty Planning 8 Health Exacerbation 9 Joint Pain 10 Needing Help 12 Afraid of and Adverse Reaction 13 Concerned About Future 15 Loss of Autonomy 17 Difficulty in Usual Activities 18 Fear of Death 21 Fear of Illnes 22 Weakness 24 Bothered by Immunoglobulins 28 Perception as Sick 29 Embarrassed 30 Becoming Infected 31 Troubled by Other Patients 32 Tired
	GSS	2 Dietary Changes 4 Diarrhea 14 Limited by Diarrhea 26 Skin Diseases
	RF	6 Cough 7 Unable to Provide Care 11 Run Out of Medications/ Immunoglobulins 16 As Contagious 19 Limited by Cough 20 Isolated 23 Difficulty in Sexual Relations 25 Limitation Upon Leisure Activity 27 Difficulty in Relationships

CVID: Common variable immune deficiency, **EF:** Emotional functioning, **RF:** Relational functioning, **GSS:** Gastrointestinal and skin symptoms, **QoL:** Quality of life.

RESULTS

Demographic and Clinical Findings of the Study Participants

Fifty patients with confirmed diagnosis were enrolled in the study between October 2019 and January 2020. The majority of the patients 64% (n=32) were males, with a mean age of the patients was 36.68 ± 13.2 years. 88% of patients (n=44) were younger than 50 years of age and 56% (n=28) had a body mass index (BMI) within the normal range. Additionally, 56% of patients (n=28) had less than 13 years of education. The median duration of disease of the patients was 52.5 (6-384) months. The majority of the patients 86% (n=43) received IVIG treatment. The median number of reported infections within 3 and 12 months before participation in the test was 1 (min-max: 0-3) and 3 (min-max: 0-12), respectively. The main clinical and demographic features are summarized in Table II.

Content Validity

To establish consensus for content validity beyond the standard error of proportion ($P < 0.05$) the content validity index (CVI) required was ≥0.70. In the first evaluation by ten experts our CVI was 0.80 for the initial 32, with 26 of them scoring an acceptable CVI for inclusion. The remaining 6 items were discussed, missing concepts identified and a final CVI employed to determine inclusion. Afterwards it was applied to the pilot group(n=5), who reported that all 32 items were clear, understandable and applicable. Then, we applied the questionnaire to 50 patients.

Feasibility

50 patients completed the questionnaire in approximately 10-15 minutes. Our missing response rate was 0.25% for all questionnaire items. Three patients left the item 23 blank, which pertained to sexuality.

Reliability

The instrument demonstrated good internal consistency in 50 patients [Cronbach's alpha, QoL Global 0.92, emotional functioning (EF): 0.91, relational functioning (RF): 0.77]. The GSS (gastrointestinal and skin symptoms) subscale consists of 4 items, 2 of them are related to the diarrhea, 1 related to skin diseases and 1 related to dietary changes. The Cronbach's alpha value was 0.47 when considering all these 4 items. However, when considering only items 4 and 14 which directly deal with bowel symptoms, Cronbach's alpha value was 0.80.

Table II: Main demographic and clinical features compared with the index study.

	Türkiye n=50	Italy n=118
Demographic characteristics		
Female/Male, n (%)	18/32 (36/64)	72/46 (61/39)
Age, years (mean ± SD)	36.68 (13.2)	NA
Age ≤ 50 years, n (%)	44 (88)	66 (56)
Age > 50 years, n (%)	6 (12)	52 (44)
Education ≤ 13 years, n (%)	25 (50)	31 (26)
Clinical characteristics		
IVIG, n (%)	43 (86)	105 (89)
SCIG, n (%)	7 (14)	13 (11)
BMI ≤ 18.5, n (%)	6 (12)	9 (7)
BMI 18.6- 24.9, n (%)	28 (56)	67 (57)
BMI ≥ 25, n (%)	16 (32)	42 (36)
Disease duration, months (median, min-max)	52.5 (6-384)	NA
Number of infections within 3 months (median, min-max)	1 (0-3)	NA
Number of infections within 12 months (median, min-max)	3 (0-12)	NA

SD: Standard deviation, **IVIG:** Intravenous immunoglobulin, **SCIG:** Subcutaneous immunoglobulin, **BMI:** Body mass index, **NA:** Not available

Convergent Validity

Correlations between the dimensions of CVID-QoL and SF-36, PtGA, PhGA were presented in Table III. QoL global, EF and RF scores exhibited good and moderate correlations with similar dimensions of SF-36. Three dimensions and QoL global showed a good correlation with PtGA and the correlation between PtGA and PhGA was also significant (r value=.541, p<0.001). Additionally, physical component summary (PCS) and mental component summary (MCS) total scores showed a good correlation with the QoL scores. (r=-.781, p<0.001; r=-.778, p<0.001).

Discriminatory Validity

The comparison of the patients' QoL scores percentages with the number of infections within 3 months and 12 months is summarized in Figure 2A,B. Patients who experienced more than one infection within 3 months had significantly higher scores of QoL-global (p=0.038), EF (p=0.045) and RF (p=0.028). Although the number of infections within the 12 months was not statistically different, we observed that those who had more infections had higher QoL-global(p=0.108), EF (p=0.106) and RF (p=0.230) scores.

Reproducibility

The instrument was re-applied to 26 patients of the participants 14-21 days later. The scores were correlated in repeated measurement in different visits. QoL-global, ICC=0.80 (95% CI 0.56-0.91) p<0.001; EF, ICC=0.78 (95% CI 0.51-0.90) p<0.001; RF, ICC=0.82 (95% CI 0.59-0.92) p<0.001; GSS, ICC=0.89 (95% CI 0.76-0.95) p<0.001.

Floor and Ceiling Effects

Overall, 43.8% (n=700) of all replies was '0=never' and 5.5% (n=88) were '4=always'. The lowest score (the best QoL score) in the whole group was 1 in 1 patient. The highest score (the lowest QoL) was 89 in 1 patient. The 25th and 75th percentiles of the QoL global were 21 and 51.5, respectively. The questions most frequently answered as 'often' and 'always' (≥ 30% of the entire group) were related to cough, difficulty in usual activities, feeling tired, fear of illness, and fear of becoming infected. The questions answered as 'never' were about fear of death, troubled by other patients, being limited by cough, and being contagious by ≥ 70% of the entire group.

Table III: Correlations of the CVID QoL-TR scores with the SF-36.

	CVID QoL Global	Emotional functioning	Relational functioning	Gastrointestinal and skin symptoms
SF-36				
Physical functioning	-.554**	-.504**	-.461**	-.496**
Role-physical	-.613**	-.631**	-.472**	-.287*
Bodily pain	-.564**	-.582**	-.550**	-.267
General health	-.533**	-.541**	-.456**	-.257
Vitality	-.535**	-.551**	-.394**	-.465**
Social functioning	-.730**	-.713**	-.666**	-.340*
Role-emotional	-.503**	-.517**	-.372**	-.305*
Mental health	-.606**	-.607**	-.498**	-.400**
Physical component summary (PCS)	-.781**	-.789**	-.655**	-.404**
Mental component summary (MCS)	-.778**	-.782**	-.639**	-.477**
GA				
PhGA	.351*	.300*	.365**	.047
PtGA	.782**	.758**	.744**	.337*

QoL: Quality of life, SF-36: short form-36, **GA:** general assessment, **PhGA:** physician general assessment, **PtGA:** patient general assessment

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

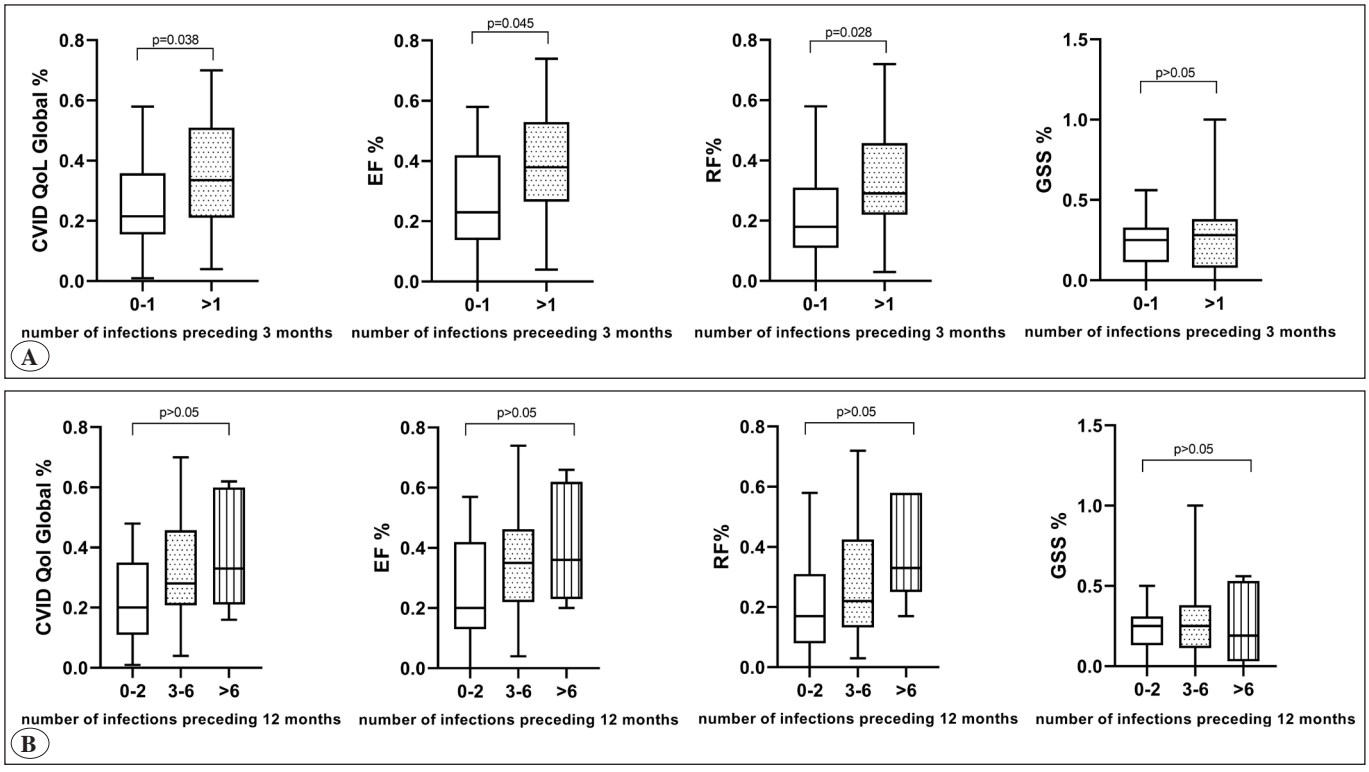

Figure 2. Number of infections and CVID QoL, EF, RF, GSS scores. Patients were divided according to the number of infections within 3 months **(A)** and within 12 months **(B)**. P values of CVID QoL global, EF, RF scores within 3 months between 0-1 infection and >1 infection were 0.038, 0.045, 0.028 respectively. P values of CVID QoL global, EF, RF scores within 12 months between 0-2 infections, 3-6 infections and >6 infections were p>0.05.

CVID: *Common variable immune deficiency;* ***EF:*** *Emotional functioning;* ***RF:*** *Relational functioning;* ***GSS:*** *Gastrointestinal and skin symptoms;* ***QoL:*** *Quality of life.*

Factor Analysis

In the current study, factor analysis did not show the three-factor structure (EF, RF, GSS) as determined in the index study. For the GSS subscale, items 4 and item 14 related to the bowel symptoms were distinguished from items 2 'dietary changes' and item 26 'skin symptoms. In the RF subscale, items 11 'run out of medications' and item 16 'as contagious', and items 6 'cough' and 25 'limitation of leisure activity' were distinguished from the other items in the RF dimension.

General QoL Assessment of the Patients

We observed that the median QoL scores in the entire patients group were 32 (min-max: 1-89). Female participants reported higher scores, indicating poorer QoL (p=0.009). Patients with less than 13 years of education had higher scores compared to those with more than 13 years of education (p=0.015). Additionally, higher scores were observed in the IVIG treatment group when compared to the SCIG treatment group (p=0.005). We did not observe a significant correlation between age, BMI, duration of disease and QoL scores (p>0.05). The QoL scores of our patients, as well as those of Italian and Norwegian groups, were stratified by gender, age, education, IVIG/SCIG treatment, and BMI groups as presented in Table IV.

DISCUSSION

We validated the Turkish version of CVID-QoL-TR and its psychometric properties in the current study, which had a high response rate and received positive responses from the patients. It showed excellent reliability, good content validity, and reproducibility.

Regarding reliability, our results revealed that all items demonstrated excellent internal consistency (>0.9) and two subscales, EF and RF, exhibited good internal consistency as well (>0.7). These findings are in agreement with

Table IV: Comparisons of the CVID QoL scores between the Turkish, Italy and Norway study groups.

Characteristics	Global CVID QoL scores		
	Scores, median (min-max) Scores, mean (± SD)	Scores, mean (± SD)	Scores, mean (± SD)
	Türkiye n=50	Italy n=118	Norway n=83
Total	32 (1-89) 36.4 (20.7)	29 (16.5)	37.4 (15.3)
Female	45 (11-89) 47.38 (21.4)	31.3 (16.4)	38.6 (15.6)
Male	27 (1-66) 30.2 (17.8)	25.7 (14.2)	33.8 (14.4)
Age ≤ 50 years	33 (1-89) 37.3 (20.8)	26.5 (15.5)	37.7 (17.9)
Age > 50 years	24.5 (8-61) 29.8 (20.7)	32.6 (15.7)	37.1 (11.8)
Education ≤ 13 years	43 (4-89) 43.1 (21.7)	32.1 (17.5)	37.6 (18.8)
Education > 13 years	26 (1-68) 29.6 (17.6)	28.3 (15.3)	37.2 (12.1)
SCIG	21 (4-27) 17.7 (8.4)	NA	41.1 (15.7)
IVIG	37 (1-89) 39.4 (20.6)	NA	34.5 (13.5)
BMI ≤ 18.5	38.5 (21-79) 45 (22.8)	41.1 (11.4)	39.3 (3)
BMI 18.6-24.9	31 (1-89) 35.7 (21.1)	28.2 (15.8)	37 (16.2)
BMI ≥ 25	35 (4-68) 34.3 (19.7)	28 (15.9)	35.5 (15.2)

CVID QoL scores are presented as median (min-max) and mean (SD) in Turkish study group, mean (SD) in Italian and Norwegian group. ***CVID:*** *Common variable immunodeficiency,* ***SD:*** *Standard deviation,* ***SCIG:*** *Subcutaneous immunoglobulin,* ***IVIG:*** *Intravenous immunoglobulin,* ***NA:*** *Not available.*

the results (0.82, 0.84) of the index study (9) and are similar (0.91, 0.77) to the findings of the Norwegian adaptation study (15). However, the GSS subscale did not achieve the acceptable internal consistency. Consisting of only four items, these elements were not highly related to each other. This may be one of the reasons for the low internal consistency observed. However, when we considering only two items (4 and 14) related to the bowel symptoms, it exhibited good internal consistency, similar to the findings of the Norwegian adaptation study (15). Another possible reason we considered was that our sample group was small to establish construct validity (20). Additionally, cutaneous problems are not as commonly observed as gastrointestinal manifestations. Generally autoimmune skin problems and case based cutaneous diseases are observed (21-23). Conversely, Ballow et al. developed a new disease specific tool for primary antibody deficiencies, which did not include any questions about skin problems (24). Therefore, we may consider that dermatologic features do not have an important impact on QoL of CVID patients, but more comprehensive studies are necessary to confirm this. Furthermore, consistent with results of index study and Norwegian cultural adaptation (9,15) test–retest reliability results showed that CVID-QoL-TR stated excellent reliability in short-term repetition. This demonstrated that results from the Turkish version of CVID-QoL is reproducible, supported it can be used as a patient-reported outcome tool.

Content validity refers to an ability of tools to accurately assess the intended area of interest and the conceptual definition of its structure (20). During the assessment of content validity, we determined that our CVI was acceptable. However, content validity ratio did not initially reach the threshold of 0.7 for six items. Subsequently, minor adjustments were made to these six items while maintaining the overall structure of the tool. The final version of tool was approved. We believe that these findings contributed to establishing the content validity of the tool.

Convergent validity assesses the extent to which a questionnaire/ tool measures what it is designed to measure (25). To examine the convergent validity of the CVID-QoL-TR, we used SF-36 as a comparative tool. SF-36 is a well-known QoL scale, translated and validated in Turkish and used in various diseases (26,27). Good correlations were found between QoL global, EF and RF subscales of the CVID-QoL-TR with certain items of the SF-36. QoL scores correlated strongly with both SF-36's physical and mental health domains. Quinti et al. showed good convergent validity for the EF and RF subscales correlating with conceptually similar dimensions of SF-36 (9). Andersen et al. reported similar findings with the WHQOOL BREF (15). Discriminant validity assesses the ability of a tool/ questionnaire to detect true differences and discriminate between the other tools or changes. It indicates that the two things/measure that should not be related are actually irrelevant (20). Our results showed that the QoL, EF, RF scores were higher in the patients complaining of more than one infection within 3 months before the study. Quinti et al reported that frequency of infections both within 3 months and 12 months before the study had an impact on the quality of life. We did not observe this association within 12 months before the study. We can speculate that this might be related to the questionnaire seeking answers to questions about the last 3 months and 12 months is a longer duration to recall.

Factor analysis is a multivariate statistical method used to identify a small number of conceptually significant new variables (factors or dimensions) by combining a large number of related variables intended to measure the same underlying structure or a particular property (28,29). More accurate factor analyses suggest that the sample size should consist of least 3-5 times more number of items than the number of variables (30). In the current study, we could not conduct factor analysis due to the relatively small sample size. However, we we were able to perform factor analysis on the GSS and RF subscales, as they consist of 4 and 9 items, respectively. We observed that in the GSS subscale, items 4 and 14, related to bowel symptoms were distinct from the item 2 'dietary changes' and item 26 'skin symptoms. In the RF subscale, items 11 'run out of medications' and item 16 'as contagious', as well as items 6 'cough' and 25 'limitation of leisure activity' were distinguished from the other items in the RF dimension. However, the EF and QoL global contain more items than can be adequately analyzed with our sample size of 50 participants. Although factor analysis did not confirm the existence of three distinct factors the strong correlation with SF-36, high reliability, reproducibility and a high response rate indicate that the CVID-QoL-TR instrument is valuable. We believe that factor analysis can be re-evaluated as the instrument is used in future studies.

We observed that being female were negatively associated with QoL. This finding was similar to the information from other CVID QoL studies (9,12,14). Receiving IVIG treatment was the second factor associated with poor QoL, which was also consistent with the previous studies (9,12). We observed a better quality of life in patients with more than 13 years of education, similar to the findings of previous studies. We did not observe any association between BMI, age and QoL in our study. This might be related to the ethnic differences. Our QoL scores were not normally distributed, but the Italian and Norwegian groups showed that their findings were normally distributed (Table IV). Our study group achieved similar mean CVID QoL scores to the Norwegian group while being higher than Italian group. 43.7% of all replies were 0 and our floor and ceiling effects indicated better QoL. Differences in the results of our study group compared to the other groups may be explained by the variation in the demographic features among the study groups. Our study group had a higher proportion of male and younger patients, and the education levels of our patients were lower than those of the participants in other study groups. Furthermore, this might be associated with low socioeconomic status or other cultural differences that could not be differentiated using disease-specific tools. Finally, we believe that it is not suitable for comparison.

Our study had limitations. One of them was the low number of adult CVID patients included in the study, despite being one of the largest centres in Türkiye. Therefore, the analysis did not include three factors as in the index study.

CONCLUSION

A CVID disease specific questionnaire is necessary to better evaluate the disease burden on the patients. Our study indicated that CVID-QoL-TR was reliable, useful and valid for measuring QoL in CVID patients. It is recommended to investigate its stability by applying it to larger patient groups and further consideration on factor analysis. Additionally, future evaluations of QoL in CVID, either with this CVID-QoL-TR in other Turkish patients or through translations into other languages, can facilitate the improvement of the knowledge about burden of CVID disease burden on individuals.

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Conflicts of interest

Authors state that there is no conflict of interest about this study.

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