

# Evaluation of Health Status and Quality of Life in Patients Using Intravenous and Subcutaneous Forms of Immunoglobulin Replacement

Intravenöz ve Subkütan İmmünoglobulin Replasman Tedavisi Kullanan Hastalarda Sağlık Durumu ve Yaşam Kalitesinin Değerlendirilmesi

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## Abstract

**Objectives:** Health-related quality of life (HRQoL) is an emerging field of research in primary immunodeficiency (PID) patients. PID patients' quality of life worsens as a result of their considerable disease load causing limited capacity to work and attend school, as well as participation in routine physical activities. The aim of this study was to analyze the demographics, treatment satisfaction, treatment-related side effects, health status and HRQoL of adult PID patients using different immunoglobulin replacement methods.

**Materials and Methods:** In this prospective, cross-sectional research, 53 adult patients, who had been diagnosed with PID and treated with IgRT, were included. The Euro-QoL 5-D (EQ-5D) and Medical Outcomes Study Short Form-36 (SF-36) scales were used to evaluate health status and HRQoL.

**Results:** The study included 53 patients with a median age of 32 (IQR: 24-45) years. Thirty-three (62.2%) patients were female. Twenty-three individuals received intravenous immunoglobulin (IVIg) and 30 subcutaneous immunoglobulin (SCIg). There was no significant difference in side effects between SCIg and IVIg. According to the EQ-5D results, anxiety/depression was the most problematic area to deal with. Patients' median SF-36 scores were significantly lower ( $p<0.005$ ) than healthy Turkish population norms in all categories (except for mental health). For physical functioning, physical role difficulty, emotional role difficulty, and vitality, the median scores of the SCIg group were similar to those of the healthy population.

**Conclusion:** Given that individuals receiving SCIg therapy have a comparable quality of life as the general population, employing SCIg in appropriate and chosen patients may improve quality of life by allowing patients to be more independent. Patients with PIDs should have regular HRQoL assessments to ensure that they are receiving sufficient psychosocial care.

**Key Words:** Health Status, Quality of Life, Primary Immunodeficiency, IVIg, SCIg

## Öz

**Amaç:** Sağlık ilişkili yaşam kalitesi (HRQoL), primer immün yetmezlik (PİY) hastalarında giderek daha çok araştırılan bir konu olarak karşımıza çıkmaktadır. PİY'lere bağlı ortaya çıkan önemli hastalık yükü hastaların çalışma ve okul hayatına dahil olma, rutin fiziksel aktivitelere katılımını olumsuz olarak etkileyerek yaşam kalitelerini düşürmektedir. Bu çalışma ile farklı immünoglobulin replasman tedavisi (IgRT) formlarını kullanan yetişkin PİY hastalarının demografik özelliklerini, tedavi memnuniyetini, tedaviye bağlı yan etkileri, sağlık durumunu ve yaşam kalitesini değerlendirmek amaçlanmıştır.

**Gereç ve Yöntem:** Bu prospektif, kesitsel araştırmaya, PİY tanısı ile takip edilen ve IgRT alan 53 erişkin hasta dahil edilmiştir. Sağlık durumunu ve yaşam kalitesini değerlendirmek için Euro-QoL 5-D (EQ-5D) ve Medical Outcomes Study Short Form-36 (SF-36) ölçeklerinin Türkçe versiyonları kullanıldı.

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Received/Geliş Tarihi: 03.12.2021 Accepted/Kabul Tarihi: 01.03.2022

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Journal of Ankara University Faculty of Medicine is published by Galenos Publishing House.

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**Bulgular:** Çalışmaya medyan yaşı 32 (IQR: 24-45) olan 53 hasta dahil edildi. Otuz üç (%62,2) hasta kadındı. Yirmi üç kişiye intravenöz immünoglobulin (IVIG) ve 30 subkütan immünoglobulin (SCIG) verildi. SCIG ve IVIG arasında yan etkiler açısından anlamlı bir fark yoktu. EQ-5D sonuçlarına göre kaygı/depresyon en sorunlu alandı. Hastaların medyan SF-36 puanları, tüm kategorilerde (ruh sağlığı hariç) sağlıklı Türk popülasyonu normlarından anlamlı derecede düşüktü ( $p<0,005$ ). Fiziksel işlevsellik, fiziksel rol güçlüğü, duygusal rol güçlüğü ve canlılık için SCIG grubu medyan puanları sağlıklı popülasyona benzerdi.

**Sonuç:** SCIG tedavisi alan bireylerin genel popülasyonla benzer bir yaşam kalitesine sahip olduğu göz önüne alındığında, uygun ve seçilmiş hastalarda SCIG kullanılması, hastaların daha bağımsız olmasına izin vererek yaşam kalitesini iyileştirebilir. PİY'li hastalarda, yaşam kalitesi düzenli olarak değerlendirilmeli ve yeterli psikososyal bakım sağlanmalıdır.

**Anahtar Kelimeler:** Sağlık Durumu, Yaşam Kalitesi, İmmünoglobulin Replasman Tedavisi, IVIG, SCIG

## Introduction

Quality of life (QoL) is a term that refers to an individual's personal satisfaction with his/her adaptation to life and represents the personal reactions to the diseases's physical, mental, and social consequences (1). The term "health related QoL (HRQoL)" refers to a multifaceted concept that attempts to describe the impact of a disease on a patient's life. The simplest definition of HRQoL is "perceived health". The patient's perception and functional impairments as a result of the disease are two main factors that have an impact on the HRQoL (2).

The development of more treatment options for chronic illnesses has prolonged patient survival, but in this situation the patient has to live with the disease. Primary immunodeficiencies (PIDs) are chronic diseases, including a heterogenous group of disorders. PIDs may manifest with recurrent/severe infections, autoimmune disorders, allergic diseases, autoinflammation, lymphoproliferation, or malignancies (3). As a result, PID patients have a significant disease burden. Impaired patients' ability to work and attend school, as well as participation in routine physical activities, all contribute to a decline in PID patients' QoL. The deterioration in QoL is often worsened by diagnostic delays and disease-related comorbidities (4). HRQoL is a growing area of investigation in patients with PID.

A lifelong immunoglobulin replacement treatment is necessary for certain patients with PID. Subcutaneous and intravenous immunoglobulin (SCIG and IVIG) replacement therapies are both effective in avoiding infections. However research data shows that patients who receive these treatments have a worse QoL in terms of mental and physical health (5).

The purpose of this study was to assess the demographic characteristics, treatment satisfaction and treatment-related side effects, health status and HRQoL of adult patients with PID who were using different methods of immunoglobulin replacement therapy.

## Patients and Methods

### Patients and Study Design

This prospective, cross-sectional study included 53 adult patients who were diagnosed with PID and treated with immunoglobulin replacement in Hacettepe University Faculty of Medicine, Department of Pediatric Immunology. Between June and September 2021, participants were questioned at outpatient control visits. Each patient provided informed consent to participate in the study. Socio-demographic data ascertained included age, gender, BMI and education level, economic status, number of hospital admissions in the preceding year, number of oral or intravenous antibiotic use episode in the preceding year, side effects experienced during immunoglobulin replacement therapy, degree of satisfaction with the immunoglobulin form used, and the reason for preference of that immunoglobulin form. This study was approved by the Ethics Committee of Hacettepe University Faculty of Medicine (GO 21/1238).

### Outcome Measures

The Euro-QoL 5-D (EQ-5D) scale was used to evaluate health status and HRQoL. The EQ-5D assesses health status in terms of five dimensions of health including mobility, self-care, usual daily activities, pain/discomfort, and anxiety/depression. A triple Likert scale was used for each item on the measure. It is also possible to determine the health benefit index score by looking at the distribution of responses to these dimensions. The second section of the EQ-5D questionnaire is a typical vertical 20-cm VAS calibrated from 'the worst health you can imagine' (score 0) to 'the best health you can imagine' (score 100) at the apex.

Patients are asked to mark an X on the scale to reflect their current state of health and enter the result in an adjacent box. The EuroQoL working group created the EQ-5D in 1990 (6). Eser et al. (7) investigated the reliability and validity of Turkish and established community norm values in 2007.

HRQoL was assessed using the Medical Outcomes Study Short Form-36 (SF-36), a commonly used generic scale. Ware and Sherbourne designed the SF-36 in 1992 (8), and a Turkish reliability and validity assessment was conducted in 1999 (9). The SF-36 is a self-report scale that covers eight dimensions

of health using 36 items. These categories include physical functioning, social functioning, role difficulties (physical and emotional), mental health, vitality, pain, and overall perception of health. The scale measures health on a scale of 0 to 100, with a higher score indicating better health. Demiral et al. (10) defined SF-36 community norm values for Turkish society in 2006.

### Statistical Analysis

The study's demographic data were represented as a percentage or as a number. Categorical variables were compared using the chi-square or Fisher-Exact test, and numerical variables using the Mann-Whitney U test, a non-parametric test for two-group comparisons, or the Kruskal-Wallis test for three-group comparisons. The t-test was used to compare patients on characteristics such as gender, education level, economic status, and immunoglobulin forms used. The single value t-test was used to compare the patients' QoL scale scores to community norm values. The statistical analysis was carried out using the SPSS 21.0, and the graphics were created using the Prism 5.0 program.

## Results

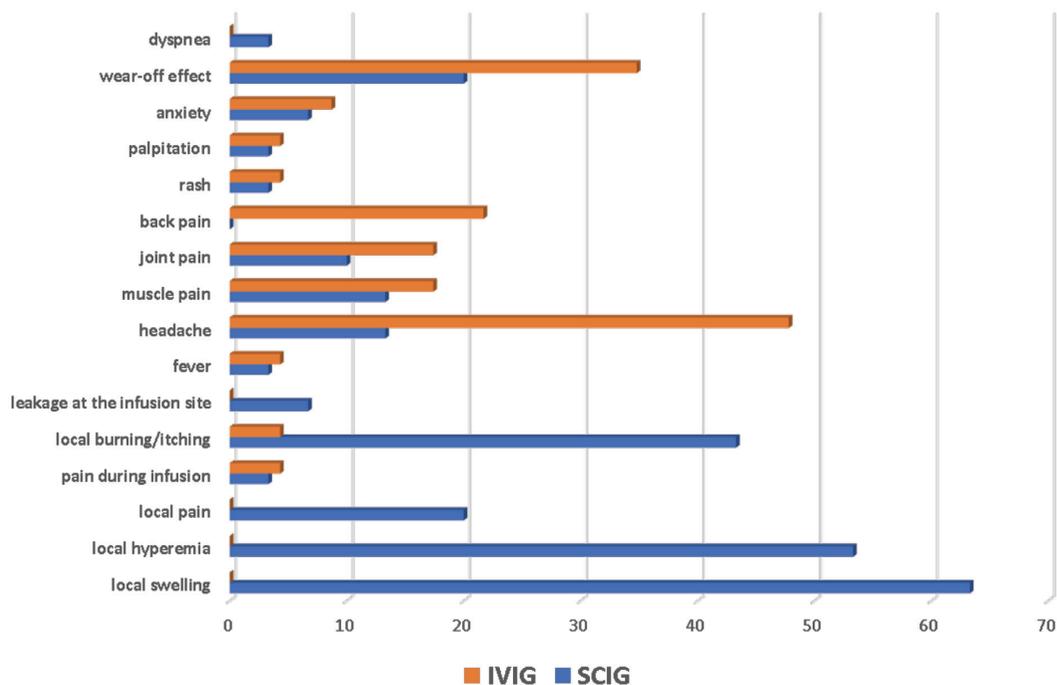
### Socio-demographic and Clinical Characteristics

The research enrolled 53 individuals with a median age of 32 years (IQR: 24-45). Thirty-three patients (62.2%) were female. There were 23 patients using IVIG, 21 receiving SCIG,

and 9 using facilitated SCIG (fSCIG). Because the fSCIG group had a limited number of patients, analyzes were conducted by combining the SCIG and fSCIG groups. Table 1 summarizes the socio-demographic and clinical characteristics of the patients. In groups receiving SCIG and IVIG, the distribution of gender, diagnosis, BMI, education level, and economic status was similar.

In terms of side effects during immunoglobulin replacement therapy (IgRT), there was no significant difference between the SCIG and IVIG groups. No side effects were reported by 35.8% of individuals. Figure 1 presents IgRT-related side effects in detail. Local side effects such as swelling (63.3%), hyperemia (53.3%), and burning/itching (43.3%) were the most often reported in the SCIG group. The most frequently reported side effects in the IVIG group were headache (47.8%), wear-off effect (34.8%), and back pain (21.7%). There was no risk factor identified in the logistic regression analysis for the emergence of adverse effects in patients receiving IgRT.

The patients' level of satisfaction with the immunoglobulin form they used was assessed using a visual analogue scale ranging from 0 to 10. The SCIG group had a median score of 9 (8-10), whereas the IVIG group had a median score of 8 (7-9), with no statistically significant difference in scores between the groups. The patients were questioned if the immunoglobulin form they used was their own preference or a doctor's suggestion. The proportion of patients who preferred the SCIG form was 36.7%; the rate for those who preferred the IVIG form was 17.4 %; the difference was not statistically significant



**Figure 1:** Distribution of adverse events reported by patients in the IVIG and SCIG groups

SCIG: Subcutaneous immunoglobulin, IVIG: intravenous immunoglobulin

(Table 2). The reasons why patients preferred the immunoglobulin forms they utilize are summarized in Figure 2. The most often stated reason for selecting the SCIG form is a reduction in the frequency of hospital visits and independence and autonomy; the most commonly quoted reason for choosing the IVIG form is a reduction in infections, less local side effects.

### Assessment of Health Status

According to the EQ-5D results, 79.2% of the patients reported no problems in mobility, 98.1% in self-care, 73.5% in usual daily activities, 62.2% in pain/discomfort, 62.2% in anxiety/depression. There was no difference in areas of difficulty between the IVIG and SCIG groups. Anxiety/depression was the most problematic area to deal with. Table 3 displays the distribution of EQ-5D answers. There was no significant differences in mean or median values for the EQ-5D health index or VAS score between the SCIG and IVIG groups. The EQ-5D health index score for the entire patient group was  $0.88 \pm 0.14$ , which was similar to the Turkish population norm values ( $0.8 \pm 0.1$ ).

### Assessment of Quality of Life

Figure 3 illustrates the SF-36 scale scores of patients in the SCIG and IVIG groups and healthy Turkish population. Compared to healthy Turkish population norm scores, patients' median scores were significantly lower ( $p < 0.005$ ) in all categories (except for mental health). However, when the IVIG and SCIG groups were compared with Turkish norm values individually, the SCIG group median scores were found to be similar to the healthy population in the categories of physical functioning, physical role difficulty, emotional role difficulty, and vitality ( $p = 0.059 - 0.319$ ). Patients received the highest score in the physical functionality category, but the lowest score in the overall perception of health. The groups were compared to one another and to the normative standards of Turkish society. The SCIG group's median scores for emotional role difficulties ( $p = 0.037$ ), and social functioning ( $p = 0.006$ ) were higher than those in the IVIG group.

### Discussion

QoL and health status in PIDs have previously received little attention in our country. In this study, we analyzed the

**Table 1: Demographical characteristics of the patients**

	Total (n=53)	SCIG (n=30)	IVIG (n=23)	P
<b>Male/female</b>	20/33	11/19	9/14	0.854
<b>BMI, n (%)</b>				
Underweight	7 (13.2)	5 (16.7)	2 (8.7)	0.069
Normal	32 (60.4)	20 (66.7)	12 (52.2)	
Overweight	10 (18.9)	2 (6.7)	8 (34.8)	
Obese	4 (7.5)	3 (10)	1 (4.3)	
<b>Diagnosis, n (%)</b>				
CID	3 (5.7)	-	3 (13)	0.092
CVID	39 (73.9)	22 (73.3)	17 (73.9)	
XLA	2 (3.8)	2 (6.7)	-	
Hyper IgM	4 (7.5)	4 (13.3)	-	
Others	5 (9.4)	2 (6.7)	3 (13)	
<b>Education level n (%)</b>				
Primary	5 (9.4)	3 (10)	2 (8.7)	0.323
Secondary	4 (7.5)	2 (6.7)	2 (8.7)	
High school	16 (30.2)	12 (40)	4 (17.4)	
University	28 (52.8)	13 (43.3)	15 (65.2)	
<b>Economic status, n (%)</b>				
Low income	12 (22.6)	9 (30)	3 (13)	0.066
Middle income	32 (60.4)	14 (46.7)	18 (78)	
High income	9 (17)	7 (23.3)	2 (8.7)	
<b>Side effects during</b>				
IgRT, n (%)	34 (64.2)	20 (66.7)	14 (60.9)	0.663

BMI: Body mass index, CID: Combined immunodeficiency, CVID: Common variable immunodeficiency, IgRT: Immunoglobulin replacement therapy, IVIG: Intravenous immunoglobulin, SCIG: Subcutaneous immunoglobulin, XLA: X linked agammaglobulinemia

QoL of patients diagnosed with PID and treated with various immunoglobulin replacement approaches. When compared to the healthy Turkish population, the QoL was found to be worse in PID patients under IGRT. The HRQoL in the SCIG group was better than in the IVIG group and comparable to the healthy population.

Immunoglobulin replacement therapy, regardless of the route of administration, improves survival and mortality in patients with PID (11). This is further confirmed by our study's

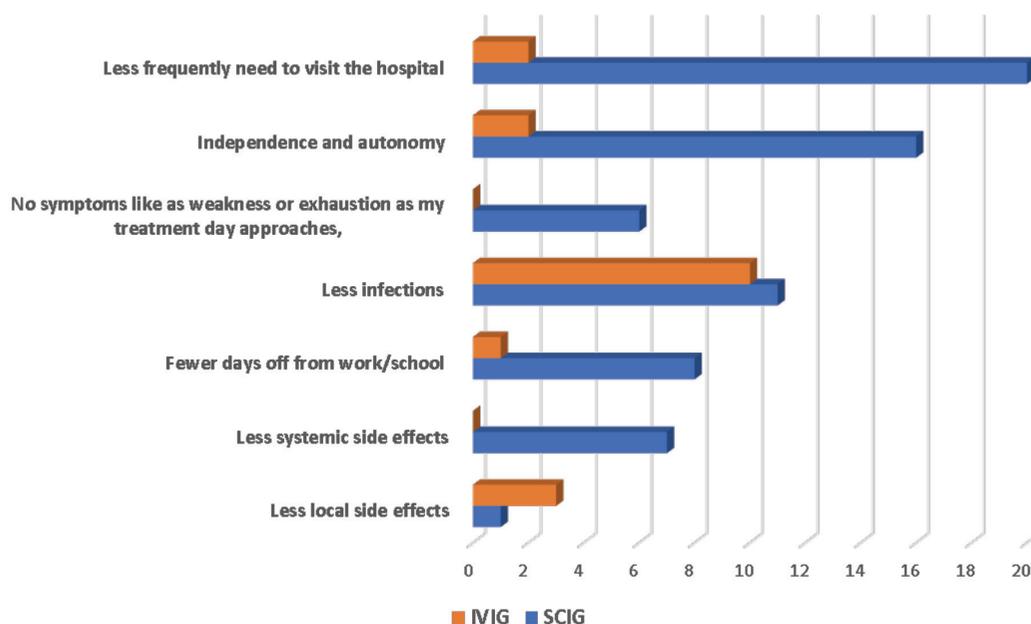
high treatment satisfaction scores for both the SCIG and IVIG groups. The patients had a variety of mild or moderate side effects during their IgRT therapy. However there was no evidence that these side effects had a negative impact on their treatment satisfaction. Treatment related local side effects were noticed more frequently in the SCIG group than in the IVIG group, as expected; headache, wear off effect, and back pain were observed more frequently in the IVIG group. There were no risk factors identified that may have predicted the occurrence of side effects.

**Table 2: Treatment selection and satisfaction of patients with their treatment method**

	Total	SCIG		IVIG		p
	n	%	n	%	n	
Doctor's advice	38	71.7	19	63.3	19	0.123
Patient's choice	15	28.3	11	36.7	4	
Satisfaction level with the Ig form	9 (8-10)	9 (8-10)	8 (7-9)			0.052

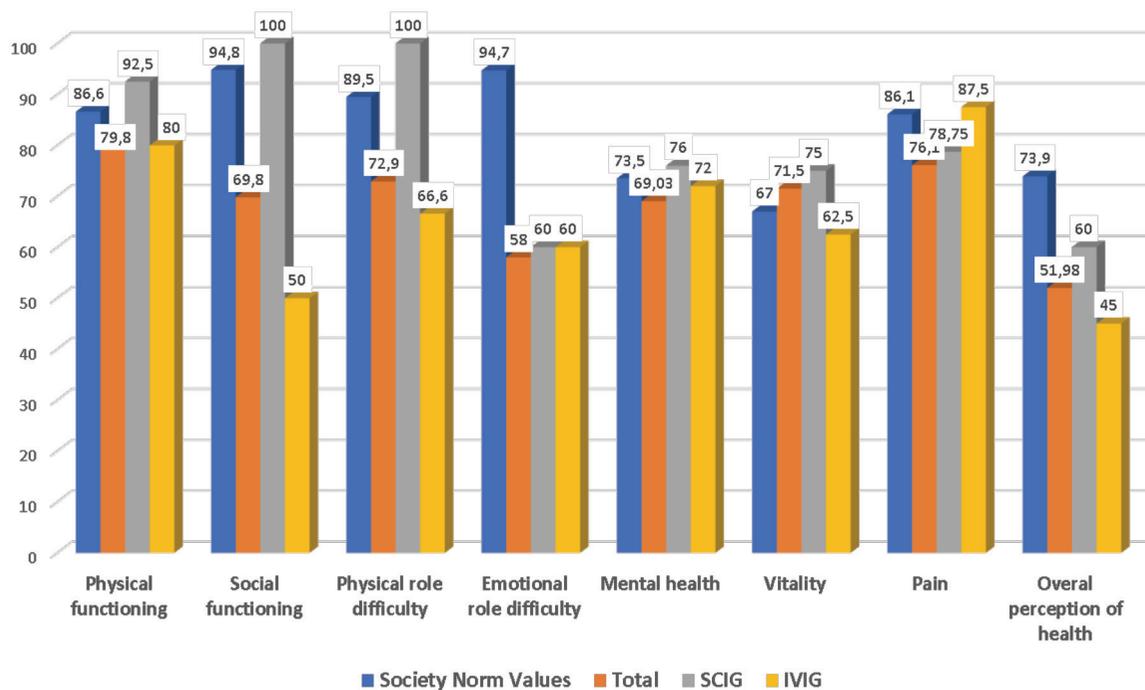
**Table 3: Distribution of EQ-5D answers in SCIG and IVIG groups**

	SCIG			IVIG			P
	No problem	Some problems	Extreme problems	No problem	Some problems	Extreme problems	
Mobility	26 (86.7%)	4 (13.3%)		16 (69.6%)	7 (30.4%)		0.128
Self-care	29 (96.7%)	1 (3.3%)		23 (100%)			0.283
Usual daily activities	24 (80%)	6(20%)		15 (65.2%)	8 (34.8%)		0.226
Pain/Discomfort	20 (66.7%)	10 (33.3%)		13 (56.5%)	10 (43.5%)		0.45
Anxiety/Depression	21 (70%)	9 (30%)		12 (5.2%)	9 (39.1%)	2 (8.7%)	0.166
EQ-VAS score median (IQR)	87.5 (70-100)			70 (60-90)			0.052
EQ-VAS score mean±SD	82.1±16.7			73.26±16.62			0.062
EQ-5D health index mean±SD	0.91±0.10			0.84±0.18			0.074



**Figure 2: Reasons for patient preference and satisfaction in the IVIG and SCIG groups**

SCIG: Subcutaneous immunoglobulin, IVIG: Intravenous immunoglobulin



**Figure 3:** SF-36 scores of patients in the whole patient group, IVIG and SCIG groups, and healthy Turkish population norms

SF-36: Short Form-36, SCIG: Subcutaneous immunoglobulin, IVIG: Intravenous immunoglobulin

The EQ-5D scale was used as a measure to assess QoL and health status. Health status evaluation, health index, and VAS scores of patients were found to be comparable to those of the general Turkish population. The EQ-5D scale revealed that the patients experienced difficulties, particularly in the areas of anxiety and depression. In a study conducted in patients with CVID, the researchers discovered that fatigue, anxiety, and social involvement were the most crucial features impacting the QoL of the participants (12). EO-VAS and EQ-5D health index scores were higher in the SCIG group than in the IVIG group, however it did not reach statistical significance.

In the assessment of HRQoL in PID patients, combining general and disease-specific measurements is an effective strategy (5). Therefore we also used the SF-36 to evaluate HRQoL. HRQoL in the SCIG group was shown to be comparable to that of the healthy population in our study. Previous research found that switching from IVIG to SCIG enhanced HRQoL in children and their parents (13,14).

While factors such as delayed diagnosis, other chronic comorbidities, stress, unemployment, recurrent infectious episodes, and chronic lung disease have a negative impact on QoL in PIDs, factors such as home treatment, independence, treatment comfort, and convenience of treatment have a positive impact (5). The proportion of patients who chose SCIG therapy as their treatment of choice was higher in our study;

the most often cited reasons were the desire to have fewer hospital visits, independence and autonomy.

When compared to the healthy population, patients with PID scored lower in most categories on the HRQoL assessment. The patients' HRQoL was shown to be affected, particularly in the area of overall health perception, emotional role difficulty and mental health. An Italian research analyzing individuals with CVID discovered that their health condition was worse than that of normal subjects. Overall, the Role-Physical and General Health measures were associated with worse clinical status and the duration of the disease had no effect on health status (15).

Patients with primary antibody deficiency were investigated in a research from Iran. They discovered that patients had considerably lower scores on several mental and physical components, and that patients with longer follow-up periods had greater mental component scores but continued to have poor physical component scores. There was no significant correlation between sex, age, and disease types with scores similar with our findings (16).

In a research published in 2016 that analyzed the QoL in patients with primary antibody deficiency before and after IgRT, 17 adult and 8 pediatric patients were included in the study. Improvements were observed in physical role difficulties as well as in overall perception of health and social functioning following IgRT (11). In our patient cohort, however, there was no

pre-treatment evaluation, and the greatest scores were achieved in the categories of physical functioning, pain, and physical role difficulties during IgRT. Remarkably, patients using SCIG achieved scores comparable to the healthy population in many areas. Indeed, the scores for social functioning and physical role difficulties were full points and even higher than those for the healthy group.

HRQoL in PID patients was compared with normal controls and patients with other chronic diseases in a review of the published literature. The articles included standardized instruments to measure HRQoL and the results emphasized the influence of treatment administration on patient satisfaction. HRQoL is significantly affected by the route of IgRT for patients with PID (5).

## Conclusion

Considering that patients getting SCIG therapy have a comparable QoL as the general population, using SCIG in suitable and selected patients may increase the QoL by allowing the patients being more independent. To improve the patient's well-being and reduce the burden of the disease on everyday life, it is necessary to further analyze the factors that influence HRQoL. The patients encountered problems, notably with anxiety and depression. Health-related quality-of-life assessments on patients with PIDs should be conducted on a regular basis to assure that they are receiving proper psychological care, according to our findings. Identifying screening and supportive treatment options for patients with PID will enhance their QoL and their emotional, physical, and social well-being, as well as their overall health.

## Acknowledgments

We thank our nurses Meliha Erol and Feride Özkan for their invaluable support and care for patients with PID.

## Ethics

**Ethics Committee Approval:** This study was approved by the Ethics Committee of Hacettepe University Faculty of Medicine (GO-21/1238).

**Informed Consent:** Informed consent was taken from all patients and/or their parents as well.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Design: S.E., I.T., Data Collection or Processing: S.E., H.N.B., A.A., Analysis or Interpretation: S.E., A.A., Literature Search: S.E., D.Ç., I.T., Writing: S.E., I.T., H.N.B., A.A., D.Ç.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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