

Prospective Evaluation of Quality of Life and Treatment Satisfaction in Pediatric Patients with IgG Subclass Deficiency Receiving Immunoglobulin Replacement Therapy

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Abstract

Immunoglobulin G subclass deficiency (IgGSD) is a heterogeneous antibody deficiency associated with recurrent sinopulmonary infections in children. This prospective study characterized the clinical, immunological, and genetic features of pediatric IgGSD patients receiving immunoglobulin replacement therapy (IgRT) and evaluated its impact on quality of life (KINDL-R) and treatment satisfaction (TSQM-9). Forty-four pediatric patients (30 males, 14 females; median age 78 months) started on regular IgRT were enrolled. Baseline clinical, lymphocyte-subset, and next-generation sequencing data were recorded; age-specific KINDL-R questionnaires were administered at baseline and Month 12, and treatment satisfaction was assessed with the TSQM-9 at Month 12, with all scores standardized to a 0-100 scale. Combined IgG2 + IgG3 deficiency was the most frequent pattern (34.1%), and the risk of lower respiratory tract infection was significantly higher with IgG2 deficiency ($p = 0.021$). Absolute CD3 + T-cell counts were reduced for age in 29.7% of patients, and primary immunodeficiency-associated genetic variants (e.g., NFKB1, TNFRSF13B, TCF3) were detected in 52.9% of those tested. After 12 months of IgRT, the mean KINDL-R score increased from 64.79 to 74.45 ($p < 0.001$), while TSQM-9 Effectiveness was high (79.67) and Global Satisfaction was comparatively lower (59.09), reflecting the burden of intravenous administration. Baseline IgGSD phenotype did not significantly affect the magnitude of quality-of-life improvement ($p > 0.05$). IgGSD is a complex entity that may involve genetic variants and cellular immune defects. IgRT exerts an equalizing effect that improves quality of life regardless of baseline immunological disadvantage, but intravenous administration limits global satisfaction, supporting consideration of subcutaneous immunoglobulin and routine use of patient-reported outcome measures.

1. Introduction

Immunoglobulin G subclass deficiency (IgGSD) is classified among the predominantly antibody deficiencies within the inborn errors of immunity, a group whose clinical and laboratory boundaries continue to be refined as the underlying genetic architecture is clarified [1]. The disorder is defined serologically by a reproducible reduction of one or more IgG subclasses below the age-matched reference range in the presence of a normal total IgG concentration. This combination is diagnostically demanding because IgG1 accounts for the greater part of circulating IgG, a selective deficiency of the quantitatively minor subclasses may be entirely concealed within a normal total IgG value, and it is only through subclass-specific quantification, interpreted against age-appropriate normative data, that the defect becomes apparent [2]. Diagnosis is further complicated by the physiological maturation of the humoral compartment during childhood and by the demonstrable variability of the phenotype, which ranges from complete absence of symptoms to a severe, infection-dominated course [3].

Clinically, IgGSD ranks alongside specific polysaccharide antibody deficiency as one of the most frequent immunological substrates of recurrent respiratory infection in children [3]. Symptomatic patients typically present with repeated infections of the upper and lower airways, including otitis media, rhinosinusitis, and pneumonia. The significance of these episodes lies not only in their acute morbidity but in their cumulative effect on the developing lung: sustained or inadequately controlled airway

infection in antibody-deficient patients may culminate in bronchiectasis and other irreversible structural sequelae, which subsequently determine long-term respiratory prognosis [4,5]. Timely recognition of the underlying defect, together with a reasoned decision regarding immunoglobulin replacement therapy (IgRT), is therefore of considerable clinical consequence.

The burden imposed by this disease process, however, is not fully captured by infection counts or antibiotic exposure. Recurrent illness in a school-aged child entails repeated absenteeism, restricted participation in age-appropriate social and physical activity, and a treatment schedule that intrudes persistently upon family life. Systematic appraisal of the primary immunodeficiency literature has consistently demonstrated impairment of health-related quality of life (HRQoL) relative to healthy comparison groups [6], and studies conducted specifically in pediatric antibody-deficient cohorts have documented a heightened prevalence of emotional and peer-relationship difficulties, indicating that the psychosocial consequences of the disease extend well beyond its infectious manifestations [7]. Patient-reported outcome measures (PROMs) have accordingly assumed an established role in the evaluation of chronic disease, providing access to dimensions of well-being that are not represented by conventional clinical endpoints.

IgRT is indicated in symptomatic patients whose infectious burden persists despite conservative management, and its efficacy in reducing infection frequency is well documented. It is nevertheless important to recognize that the intervention itself carries a burden. Quality of life among patients maintained on intravenous immunoglobulin is influenced not only by the infections averted but by the practical demands of administration, including venous access, scheduled attendance at infusion units, and the resulting encroachment on daily routine [8]. For this reason, satisfaction with therapy has come to be regarded as an outcome distinct from clinical efficacy, and dedicated instruments have been developed and validated to quantify it in patients committed to lifelong replacement [9,10]. Investigations assessing HRQoL before and twelve months after the initiation of immunoglobulin G have provided valuable evidence of benefit but have drawn upon heterogeneous antibody-deficiency populations in which pediatric patients were sparsely represented [11]. Prospective data that concurrently characterize the change in quality of life and the perceived acceptability of treatment in children with IgGSD are correspondingly scarce.

The present prospective study was designed to address this deficiency. Pediatric patients commencing regular IgRT for symptomatic IgGSD were assessed at baseline and again after twelve months of treatment. Health-related quality of life was measured using the KINDL-R questionnaire, a validated generic pediatric instrument administered in age-specific modules, which resolves well-being into physical, emotional, social, and school-related domains and thereby permits improvement to be localized rather than merely aggregated [12]. Treatment satisfaction was evaluated in parallel using the nine-item Treatment Satisfaction Questionnaire for Medication (TSQM-9), which yields separate scores for effectiveness, convenience, and global satisfaction, allowing the burden of the intravenous route to be appraised against the benefit conferred [13]. Our objectives were threefold: to determine whether IgRT produces a measurable improvement in quality of life in this population; to establish whether such

improvement is conditioned by the baseline immunological phenotype; and to characterize how the treatment is judged by the patients who receive it.

2. Materials and Methods

2.1. Study Design and Patient Selection

This prospective and observational study included a total of 44 pediatric patients (age at treatment initiation ranging from 25 to 180 months) who were followed up with a diagnosis of IgGSD and initiated on regular IgRT at our Pediatric Allergy and Immunology Clinic. To comply with the age-specific cognitive validations of the administered quality of life scales, the patients were divided into three sub-cohorts: the 4–6 years age group (n = 10), the 7–13 years age group (n = 25), and the 14–17 years age group (n = 5). All patients received a standard IgRT protocol consisting of IVIG administration at a dose of 400–600 mg/kg every 3 to 4 weeks, adjusted according to individual immunoglobulin levels and clinical condition to maintain clinical efficacy.

Inclusion criteria were a confirmed diagnosis of IgGSD with levels falling below age-adjusted reference values, a history of persistent/recurrent sinopulmonary infections despite conservative prophylaxis and having received regular IgRT for at least 12 months [14]. Concomitant comorbidities (atopic dermatitis, asthma, allergic rhinitis, and food allergy) and clinical presenting symptoms were recorded using standard protocols. This study protocol was reviewed and approved by the Sakarya University Faculty of Medicine Ethics Committee (approval number E-43012747-050.04-51317-471, date 20.09.2025), and written informed consent was obtained from the parents/legal guardians of all participants.

2.2. Clinical, Immunological, and Genetic Assessment

The patients' baseline (Month 0) immunological evaluations and treatment responses at Month 12 were comprehensively analyzed. Serum immunoglobulin levels (Total IgG, IgA, IgM, IgE, and IgG subclasses) and specific antibody responses (Anti-A and Anti-B isohemagglutinins, as well as Anti-HBs, Anti-Rubella, and Anti-CMV IgG) were measured.

Comprehensive immunophenotyping of the study cohort was performed using flow cytometry. Absolute counts and percentages of standard lymphocyte subsets (CD3 + T cells, CD4 + T cells, CD8 + T cells, CD19 + B cells, and CD16 + 56+ NK cells) were evaluated according to age-specific reference ranges previously established in the Turkish population [15]. In addition, extended B-cell subsets (naive B cells, unswitched memory B cells, switched memory B cells, and CD21^{low}CD38^{low} B cells) and T-cell subsets (naive, central memory, effector memory, and terminal effector CD4 + and CD8 + T cells; recent thymic emigrants; double-negative T cells; and TCR- $\alpha\beta$ /TCR- $\gamma\delta$ cells) were documented at baseline.

Next-Generation Sequencing (NGS)-based genetic testing was initiated in all patients to elucidate immunological phenotypes at the molecular level. However, genetic analysis results for 10 patients were not yet available by the end of the study period. Therefore, only the available NGS data from 34 patients

were included in the final analysis. Systematic clinical criteria were not used to exclude these 10 patients, thus minimizing the risk of selection bias towards more severe phenotypes. The identified genetic variants were classified as immunological and non-immunological variants.

2.3. Assessment of Quality of Life and Treatment Satisfaction

Health-related quality of life (HRQoL) and treatment satisfaction were assessed using the Turkish-language versions of the KINDL-R and TSQM-9 questionnaires. The KINDL-R is a validated, age-specific instrument for evaluating HRQoL in children and adolescents and has previously been adapted and psychometrically evaluated in Turkish children [12,16]. TSQM-9 is a validated questionnaire assessing treatment satisfaction across three domains: Effectiveness, Convenience, and Global Satisfaction [13]. The use of KINDL-R and TSQM-9 has also been reported in a recent prospective Turkish cohort of patients with primary immune deficiencies receiving immunoglobulin replacement therapy [17].

The KINDL-R was administered at baseline and after 12 months of IgRT. Age-appropriate versions were used: Kiddy-KINDL-R for children aged 4–6 years, Kid-KINDL-R for those aged 7–13 years, and Kiddo-KINDL-R for adolescents aged 14–17 years. The questionnaire evaluates physical well-being, emotional well-being, self-esteem, family, friends, and school-related functioning. Negatively worded items were reverse-coded according to the standard scoring procedure, and scores were transformed to a 0–100 scale, with higher scores indicating better HRQoL. Change in quality of life was expressed as $\Delta\text{KINDL-R} = \text{Month 12 score} - \text{baseline score}$ [12,16,17].

Treatment satisfaction was assessed on Month 12 using the TSQM-9. The questionnaire consists of nine items grouped into three domains: Effectiveness (items 1–3), Convenience (items 4–6), and Global Satisfaction (items 7–9). Domain scores were calculated according to the standard TSQM-9 scoring algorithm and transformed to a 0–100 scale, with higher scores indicating greater treatment satisfaction [13,17].

2.4. Statistical Analysis

Statistical analyses of the obtained data were performed using IBM SPSS Statistics (version 27.0) software. Descriptive statistics were presented as mean $\pm$ standard deviation for normally distributed continuous variables, and as median and interquartile range (IQR) for non-normally distributed variables. Categorical variables were expressed as frequencies and percentages (%). The conformity of the data to normal distribution was evaluated using the Shapiro-Wilk test. Depending on the data distribution, either the Paired Samples t-test or the Wilcoxon Signed-Rank Test was used to compare pre-treatment (baseline) and Month 12 immunoglobulin levels and quality of life/satisfaction scores. Potential correlations between extended T and B cell memory subsets and TSQM-9 and KINDL-R scores were examined using Pearson or Spearman correlation analyses. The statistical significance level was set at $p < 0.05$ for all analyses. To account for the increased risk of Type I error due to multiple comparisons in categorical analyses and subgroup comparisons, the Benjamini-Hochberg False Discovery Rate (FDR)

correction method was applied to adjust the raw p-values. Adjusted p-values (q-values) < 0.05 were considered statistically significant. The clinical significance of the changes in KINDL-R scores was evaluated by calculating the effect size using Cohen's d. The effect size of 0.2 was considered small, 0.5 moderate, and ≥ 0.8 large.

3. Results

3.1. Demographic Characteristics and Immunological Phenotype

The demographic characteristics and IgGSD patterns of the 44 pediatric patients included in the study are summarized in Table 1. Most of the cohort consisted of male patients; 68.2% (n = 30) were male and 31.8% (n = 14) were female. The median age at the initiation of IgRT was determined to be 78 months (range: 25–180 months).

Table 1
Demographic characteristics of patients and distribution of IgG subclass deficiencies.

Characteristics	Count (n)	Percentage (%)
Gender		
Male	30	68.2
Female	14	31.8
Age (months)		
Median (Min-Max)	78 (25–180)	-
IgG Subclass Deficiency Patterns		
Isolated IgG3 Deficiency	10	22.7
IgG2 + IgG3 Deficiency	15	34.1
IgG2 + IgG3 + IgA Deficiency	9	20.5
IgG3 + IgA Deficiency	4	9.1
IgG3 + IgM Deficiency	1	2.3
Isolated IgG2 Deficiency	2	4.5
IgG2 + IgG4 Deficiency	1	2.3
IgG2 + IgA Deficiency	1	2.3
IgG2 + IgG3 + IgG4 Deficiency	1	2.3

When the immunological phenotyping results and specific deficiency patterns of the patients were examined, it was observed that combined deficiencies were quite prominent in the cohort. The most frequently encountered immunological defect was combined IgG2 and IgG3 deficiency, detected in 34.1% (n = 15) of the patients. This was followed by isolated IgG3 deficiency with a frequency of 22.7% (n = 10) and combined IgG2 and IgG3 deficiency accompanied by IgA deficiency (IgG2 + IgG3+IgA) at a rate of 20.5% (n = 9). Other patterns observed at lower rates included IgG3 + IgA deficiency (9.1%, n = 4) and isolated IgG2 deficiency (4.5%, n = 2). Furthermore, in the remainder of the cohort, deficiency patterns considered to be highly rare clinical entities, namely IgG2 + IgG4, IgG2 + IgA, IgG3 + IgM, and IgG2 + IgG3 + IgG4 deficiencies, were each detected at an equal rate of 2.3% (n = 1).

3.2. Cellular Immunity and Lymphocyte Subsets

The pre-treatment cellular immunity status of the patients was evaluated based on the absolute counts of peripheral blood lymphocyte subsets according to age-specific reference ranges (Table 2). Upon examination of the flow cytometry analyses of 37 patients with complete data, the absolute T lymphocyte (CD3+-) count was within normal limits in 70.3% (n = 26) of the patients, whereas it exhibited a significant decrease, falling below the expected age-specific reference values, in 29.7% (n = 11). T helper cells (CD3+-CD4+) and T cytotoxic cells (CD3+-CD8+) levels were preserved in most of the patients (91.9%, n = 34). Similarly, the absolute counts of B lymphocytes (CD19+) and Natural Killer (NK-CD16+/56+) cells were found to be within normal age-appropriate ranges in 91.9% and 94.6% of the patients, respectively.

Table 2
Evaluation of cellular immunity (lymphocyte subgroups) absolute levels (n = 37).

Lymphocyte Subgroups	Low n (%)	Normal n (%)	High n (%)
CD3+ -Cells	11 (29.7%)	26 (70.3%)	0 (0.0%)
CD3 + CD4+ -Cells	1 (2.7%)	34 (91.9%)	2 (5.4%)
CD3 + CD8+ -Cells	1 (2.7%)	34 (91.9%)	2 (5.4%)
CD19+ -Cells	1 (2.7%)	34 (91.9%)	2 (5.4%)
CD16/56+ -Cells	2 (5.4%)	35 (94.6%)	0 (0.0%)

3.3. Clinical Findings and Immunoglobulin Replacement Therapy Indications

The clinical presentations unresponsive to prophylactic treatment that constituted the rationale for initiating IgRT in the 44 patients included in the study are detailed in Table 3. The most frequent clinical finding was recurrent upper respiratory tract infections (URTI), detected in 50.0% (n = 22) of the patients. This was followed by recurrent lower respiratory tract infection (LRTI) episodes observed in 38.6% (n =

17) and recurrent sinusitis in 9.1% (n = 4). Rarer clinical presentations included recurrent otitis media (4.5%, n = 2) and recurrent herpes infections (4.5%, n = 2).

Table 3
Distribution of clinical findings constituting the indication for immunoglobulin replacement therapy (n = 44).

Clinical Presentation / Indication	Count (n)	Percentage (%)
Recurrent URTI	22	50.0
Recurrent LRTI / Pneumonia	17	38.6
Recurrent Sinusitis	4	9.1
Recurrent Otitis Media	2	4.5
Recurrent Herpes Infections	2	4.5
Abbreviations: URTI: Upper Respiratory Tract Infection; LRTI: Lower Respiratory Tract Infection		

Potential associations between the patients' IgGSD diagnoses and the types of infections (clinical indications) that led to the initiation of IgRT were analyzed using categorical independence tests (Fisher's Exact Test) (Table 4). The statistical analysis revealed that the risk of experiencing LRTIs was significantly higher in patients with IgG2 deficiency compared to those without IgG2 deficiency ($p = 0.021$). Specifically, 15 (88.2%) out of the 17 patients presenting with LRTI episodes had a concomitant IgG2 deficiency. Conversely, no statistically significant association was established between IgG3 deficiency or concomitant IgA deficiency (IgGSD + IgA deficiency) and any specific type of infection ($p > 0.05$).

Table 4

Association between specific IgG subclass deficiency components and immunoglobulin replacement therapy indications.

Immunodeficiency Component	Infection Type (IgRT Indication)	Patients with Both (n)	Patients with Deficiency but WITHOUT the Infection (n)	Total Patients with Deficiency (n)	P-value*
IgG2 Deficiency	Recurrent LRTI	15	14	29	0.021
	Recurrent URTI	12	17	29	0.202
	Recurrent Sinusitis	4	25	29	0.282
	Recurrent Otitis Media	1	28	29	1.000
IgG3 Deficiency	Recurrent LRTI	14	26	40	0.282
	Recurrent URTI	21	19	40	0.606
	Recurrent Sinusitis	3	37	40	0.326
	Recurrent Otitis Media	2	38	40	1.000
IgA Deficiency (Comorbid)	Recurrent LRTI	5	9	14	1.000
	Recurrent URTI	7	7	14	1.000
	Recurrent Sinusitis	2	12	14	0.581
	Recurrent Otitis Media	1	13	14	0.540
* Analyzed using Fisher's Exact Test to determine the association between the presence of a specific deficiency component and a specific clinical complaint. LRTI: Lower Respiratory Tract Infection, URTI: Upper Respiratory Tract Infection. Significant p-values (< 0.05) are bolded).					

3.4. Immunological Efficacy of Immunoglobulin Replacement Therapy

The immunological efficacy of the standardized IgRT protocol was evaluated by comparing the pre-treatment (Month 0) and 12th-month serum trough immunoglobulin levels (Table 5). While the pre-treatment mean total IgG level of the entire cohort was 854.5 ± 254.7 mg/dL (median: 841.5 mg/dL), this value exhibited a highly significant statistical increase, reaching 1255.2 ± 1082.7 mg/dL (median: 1050.0

mg/dL) following 12 months of regular replacement therapy ($p < 0.001$). This statistical elevation demonstrates that the administered weight-based IgRT protocol successfully achieved and maintained the targeted age-specific trough IgG levels.

Table 5

Serum IgG and IgG subclass-specific improvement after 12 months of IgRT treatment, classified according to baseline deficiency patterns.

Evaluation of IgG and IgG subclasses	Baseline (Month 0)	Month 12	p-value*
Total IgG (n = 44)			
Mean $\pm$ SD (mg/dl)	854.5 $\pm$ 254.7	1255.2 $\pm$ 1082.7	< 0.001
Median (IQR)	841.5 (635.2–1020.0)	1050.0 (860.5–1272.5)	
IgG2 in IgG2-Deficient Patients (n = 29)			
Mean $\pm$ SD (mg/dL)	105.7 $\pm$ 44.0	367.8 $\pm$ 133.3	< 0.001
Median (IQR)	101.0 (74.0–119.0)	336.0 (254.0–490.0)	
IgG3 in IgG3-Deficient Patients (n = 40)			
Mean $\pm$ SD (mg/dL)	24.9 $\pm$ 10.0	45.0 $\pm$ 22.3	< 0.001
Median (IQR)	25.5 (18.0–29.2)	46.5 (25.0–64.0)	
IgG4 in IgG4-Deficient Patients (n = 2)			
Mean $\pm$ SD (mg/dL)	0.4 $\pm$ 0.4	60.0 $\pm$ 60.8	0.500
Median (IQR)	0.4 (0.2–0.5)	60.0 (38.5–81.5)	
* p-values were calculated using the Wilcoxon Signed-Rank Test. SD: Standard Deviation, IQR: Interquartile Range.			

In addition to this overall improvement in total IgG levels, sub-analyses based on patients' baseline IgG subclass deficiencies revealed a highly specific immunological improvement. In patients with baseline IgG2 deficiency (n = 29), the mean pre-treatment serum IgG2 level increased from 105.7 $\pm$ 44.0 mg/dL to 367.8 $\pm$ 133.3 mg/dL at 12 months ($p < 0.001$). Similarly, in patients with IgG3 deficiency (n = 40), the mean serum IgG3 levels increased from 24.9 $\pm$ 10.0 mg/dL to 45.0 $\pm$ 22.3 mg/dL ($p < 0.001$). Although the sample size was limited (n = 2), a significant increase in absolute values was also observed in the IgG4 deficiency group (from 0.4 $\pm$ 0.4 mg/dL to 60.0 $\pm$ 60.8 mg/dL). These data clearly demonstrate that the administered IgRT preparations not only increase overall immunoglobulin levels but also successfully and biologically compensate for specific subclass deficiencies in patients.

3.5. Allergen Sensitization Profile

When evaluating atopic comorbidities accompanying the immunodeficiency picture, a large proportion of the patients (81.8%, n = 36) tested negative in allergy assessments (skin prick test or specific IgE) and were classified in the non-atopic group (Table 6). In the 18.2% (n = 8) group with positive allergic sensitization, the most frequently encountered trigger was house dust mite (11.4%, n = 5). Other specific sensitizations included grass pollen (9.1%, n = 4), animal dander (2.3%, n = 1), and food allergens (2.3%, n = 1).

Table 6
Allergic sensitization profile of the patients (n = 44).

Atopy Status and Allergen Type	Count (n)	Percentage (%)
Non-atopic (Negative Sensitization)	36	81.8
Atopic (Positive Sensitization)	8	18.2
House Dust Mite	5	11.4
Grass Pollen	4	9.1
Animal Dander	1	2.3
Food	1	2.3

3.6. Genetic Analysis Results

To investigate the genetic background of IgGSD, data from 34 patients analyzed via NGS were evaluated (Table 7). Variants associated with Primary Immunodeficiency (PID) were detected in more than half of the patients who underwent genetic testing (52.9%, n = 18). Within this group, the most common mutations were identified in the NFKB1 (8.8%, n = 3), TNFRSF13B (TACI) (5.9%, n = 2), and TCF3 (5.9%, n = 2) genes; in the remaining 32.4% (n = 11), isolated variants (n = 1 each) were detected in other rare PID genes that play critical roles in cellular immune development, antibody production, and signal transduction pathways. These other PID-associated genes were reported as PIK3CD, CARD11, IKBKB, ATM, IRF8, SAMD9, BCL11B, MBL, IKZF1, IRF2BP2, and DNMT3B, respectively. On the other hand, non-immunological variants that do not encompass a classic PID component but may contribute to the patient's overall clinical picture, autoinflammatory phenotype, or other accompanying findings were detected in 29.4% (n = 10) of the genetically analyzed patients. In this group, an MEFV gene variant associated with Familial Mediterranean Fever (n = 2) was the most frequent autoinflammatory mutation, while isolated variants (n = 1 each) were found in the TNFAIP3, PLCG2, F12, MPL, SMS, RYR1, PLG, and SLC37A4 genes in the remaining 23.5% (n = 8), which could be associated with specific clinical findings or comorbidities.

Table 7
Distribution of genetic variants detected by Next-Generation Sequencing (NGS) in patients with IgG subclass deficiency (n = 34).

Genetic Analysis Results	Count (n)	Percentage (%)
Primary Immunodeficiency Associated Variants	18	52.9
NFKB-1 Gene	3	8.8
TNFRSF13B (TACI) Gene	2	5.9
TCF-3 Gene	2	5.9
Other PID Associated Genes	11	32.4
Variants without Immunodeficiency Component	10	29.4
MEFV Gene	2	5.9
Other Clinical Findings / Genes	8	23.5
No Variants Detected	6	17.6
Total Tested	34	100.0

3.7. Changes in Quality of Life and Treatment Satisfaction

To evaluate the impact of IgRT on the general psychosocial status of patients, age-specific KINDL-R forms were administered at baseline (Month 0) and at Month 12 (Fig. 1). Likert responses provided by the patients were reverse coded for negative questions, and all scores were transformed into a standardized 0-100 scale. Four patients were excluded from the KINDL-R quality of life analysis due to inability to complete the questionnaire (three patients with intellectual disability and one patient younger than 4 years of age).

When the obtained results were examined, a highly statistically significant increase was detected in the HRQoL scores of the cohort following IgRT. While the pre-treatment (Month 0) mean KINDL-R score of the entire cohort was 64.79 ± 10.3 , this score increased to 74.45 ± 11.2 after 12 months of regular replacement therapy ($p < 0.001$). In sub-analyses based on age groups, a dramatic improvement in quality of life was recorded, particularly in the age groups of 4–6 years ($p = 0.007$) and 7–13 years ($p < 0.001$); the improvement in the 14–17 years adolescent group remained at borderline significance ($p = 0.062$), likely due to the relatively smaller sample size ($n = 5$).

To evaluate the specific satisfaction level with the administered IgRT, the results of the TSQM-9 administered to parents/patients' post-treatment (Month 12) were also standardized (0-100) and analyzed (Fig. 2). The "Effectiveness" domain, which measures the ability of IgRT to prevent/relieve symptoms, was the domain with the highest satisfaction level at 79.67 ± 13.45 points. The "Convenience" score, reflecting the ease of medication administration, was 72.60 ± 16.31 points, and the "Global Satisfaction" score, reflecting overall treatment perception and confidence, was determined as

59.09 ± 12.85 points. These data indicate that although specific symptom control is achieved, the practical challenges of the chronic intravenous treatment regimen limit the global satisfaction of the patients to a certain extent.

The potential effects of the patients' baseline IgGSD patterns on the clinical/psychosocial response to IgRT were analyzed using the Mann-Whitney U test. In these analyses, patients were grouped as those with a specific subclass defect (e.g., those with IgG2 deficiency) and those without (e.g., those with isolated IgG3 deficiency); the net increase amount (Δ Score) in KINDL-R scores and TSQM-9 satisfaction scores were compared between the groups (Table 8).

Table 8
Comparison of Quality-of-Life improvement and Treatment Satisfaction scores according to specific IgG subclass deficiency patterns

Quality of Life and Satisfaction Measures	IgG2 Deficient (n = 29) vs. Not Deficient (n = 15) (p-value*)	IgG3 Deficient (n = 40) vs. Not Deficient (n = 4) (p-value*)	IgA Deficient (n = 14) vs. Not Deficient (n = 30) (p-value*)
TSQM-9 Effectiveness Domain	0.186	0.575	0.317
TSQM-9 Convenience Domain	0.394	0.193	0.759
TSQM-9 Global Satisfaction Domain	0.753	0.709	0.277
KINDL-R Score Improvement (Δ Score)	0.877	0.341	0.344
KINDL-R 12. Month Final Score	0.223	0.173	0.424
* Data compared using the Mann-Whitney U test. KINDL-R Score Improvement represents the absolute point increase from baseline to 12 months. No statistically significant differences ($p < 0.05$) were observed between the phenotypic subgroups.			

Upon reviewing the results, the presence of IgG2, IgG3, or concomitant IgA deficiency in the patient's immunological phenotype was found not to create a statistically significant difference in the TSQM-9 Effectiveness, Convenience, or Global Satisfaction scores achieved post-IgRT ($p > 0.05$). Similarly, the net improvement scores obtained in the patients' quality of life (KINDL-R Δ Score) after treatment exhibited a homogeneous distribution across the entire cohort, independent of the IgGSD pattern ($p > 0.05$).

4. Discussion

This prospective observational study reveals the multidimensional effects of treatment on HRQoL and specific treatment satisfaction, alongside its clinical efficacy, in pediatric patients diagnosed with IgGSD and initiated on regular immunoglobulin replacement therapy (IgRT). Although the clinical characteristics

of IgGSD cohorts have frequently been described retrospectively in the literature, data combining extended immunological phenotyping, NGS-based genetic analyses, and age-specifically validated questionnaires (KINDL-R and TSQM-9) in a single prospective design remain quite limited. The most striking results of our study are the statistical association between IgG2 deficiency and lower respiratory tract infections, the genetic heterogeneity of the cohort, and the fact that the administered IgRT eliminated initial immunological disadvantages, thereby providing a homogeneous increase in quality of life across all subgroups.

Upon examining the clinical presentation of our study cohort, the most frequent reasons for admission were recurrent URTI and LRTI episodes, consistent with the literature [18,19]. When evaluating specific subclass deficiencies, combined IgG2 and IgG3 deficiency (34.1%) and isolated IgG3 deficiency (22.7%) were the most frequently observed patterns. When the relationship between the patients' immunological patterns and the types of infections forming the indication for IgRT was analyzed, the risk of experiencing LRTIs was found to be significantly higher in patients with IgG2 deficiency ($p = 0.021$). This finding perfectly aligns with fundamental pathophysiological mechanisms in clinical immunology practice, as the IgG2 subclass is a major component of the antibody response against polysaccharide antigens of encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* [20]. The impairment of this response in IgG2 deficiency leaves patients highly vulnerable to lower respiratory tract infections, highlighting the critical protective role of IgRT in this specific group. The therapeutic success of IgRT is further evidenced by the effective and targeted upregulation of the deficient IgG subclasses. Strong and statistically significant increases in mean serum IgG2 (from 105.7 to 367.8 mg/dL) and IgG3 (from 24.9 to 45.0 mg/dL) levels from the start of treatment to 12 months underscore the biological efficacy of the treatment. We hypothesize that these statistical data translate directly into clinical benefits and are a key factor behind improvements in patients' health-related quality of life (HRQoL) and the high treatment efficacy scores reported in TSQM-9.

Our comprehensive immunophenotyping results indicate that an IgGSD diagnosis may not always be an isolated antibody production defect. In our flow cytometry analyses, it is quite remarkable that absolute CD3⁺ -T lymphocyte counts fell below age-specific reference ranges in 29.7% of the patients. This cellular immunity defect may herald a broader underlying immune dysregulation or a PID picture [21]. A recent study published by Wagström et al. [22] reported a decrease in Treg cells and an increase in immune activation markers in IgGSD patients, emphasizing that IgGSD should be evaluated within a more immunologically complex disease spectrum. Indeed, our NGS analyses strongly supported this clinical suspicion. Variants in genes play roles in the cellular development of the immune system and signal transduction pathways, such as *NFKB1*, *TNFRSF13B*, and *TCF3*, were detected in 52.9% of the genetically tested patients [23]. Particularly considering the well-known strong association of variants detected in the *NFKB1* and *TNFRSF13B* genes with the pathogenesis of Common Variable Immunodeficiency (CVID), it should be kept in mind that an IgGSD picture detected in early childhood may evolve into a more severe antibody deficiency phenotype (such as CVID) in advancing age [24,25]. This data suggest that molecular genetic analysis should be a standard assessment tool in IgGSD patients accompanied by symptomatic and cellular defects.

When evaluating PROMs, which are the main focuses of our study, 12 months of regular IgRT was shown to provide a dramatic improvement in the quality of life of pediatric patients. The overall KINDL-R score, which was 64.79 on average before treatment, increased to 74.45 after treatment, and this increase is highly statistically significant ($p < 0.001$). A decrease in school absenteeism secondary to a reduction in the frequency and severity of infections, along with an increase in participation in daily activities and social life, are the primary reasons for this improvement. In sub-analyses according to age groups, significant differences were found in the 4–6 years ($p = 0.007$) and 7–13 years ($p < 0.001$) groups, whereas the increase in the 14–17 years adolescent group remained at borderline significance ($p = 0.062$), most likely attributable to the narrow sample size ($n = 5$) in this subgroup. However, it is also highly probable that the psychosocial dynamics brought about by adolescence and the emotional burden created by the awareness of having a chronic disease affected the perception of quality of life in this age group. Furthermore, the nearly 10-point mean increase in the overall KINDL-R score (from 64.79 to 74.45) corresponds to a large effect size (Cohen's $d > 0.8$), significantly exceeding the accepted Minimal Clinically Important Difference (MCID) thresholds for pediatric quality of life instruments. This proves that the statistical significance achieved is coupled with a highly perceptible, real-world clinical improvement for the patients.

The results of evaluating treatment satisfaction with the TSQM-9 questionnaire open a critical window that can guide clinical practice. A high mean score of 79.67 points was achieved in the "Effectiveness" sub-dimension, which reflects the success of IgRT in preventing symptoms. However, the "Global Satisfaction" score remaining at the 59.09 level indicates that the practical difficulties brought by chronic intravenous treatment (the stress of establishing vascular access, time spent in the hospital, and loss of workforce for parents) continue to pose a significant burden on patients and their families. As emphasized in similar studies, we believe that Subcutaneous Immunoglobulin (SCIG) therapy, which can be administered in the home environment, should be considered as a valuable alternative to increase global satisfaction and convenience, especially in pediatric cohorts experiencing vascular access problems due to IVIG administration or those with high hospital anxiety [26,27].

Another of the most original and striking findings of our study is our "cross-analysis" results. It was determined that the specific deficiency patterns patients had prior to treatment (IgG2 deficiency, IgG3 deficiency, or concomitant IgA deficiency) had no negative impact on the quality-of-life improvement and satisfaction to be derived from the administered IgRT ($p > 0.05$ for all comparisons). In other words, IgRT assumed an "equalizing" (leveling the playing field) role for the entire cohort by eliminating the clinical disadvantages stemming from the patients' genetic and immunological defects; it allowed every patient to derive optimal and homogeneous psychosocial benefit from the treatment, regardless of their presenting phenotype.

Our study has certain limitations. Being a single-center study and having a relatively small number of patients in specific subgroups (especially the adolescent cohort aged 14–17 years) may limit statistical power to certain extents. In addition, the inability to establish an "untreated placebo control group" due to the ethical and clinical necessity of IgRT is an inherent limitation stemming from the nature of the study.

Although we demonstrated a significant improvement in HRQoL, potential confounding factors such as age, gender, and the presence of atopic comorbidities (e.g., asthma, allergic rhinitis) were not entirely isolated using multivariate regression models. While the robust pre- and post-treatment paired design inherently controls for baseline patient characteristics to some extent, the complex interplay between chronic atopy and quality of life warrants future studies utilizing larger cohorts and multivariable adjustments.

5. Conclusion

IgGSD is not merely a simple antibody defect characterized by recurrent infections; it is a complex clinical entity that can be accompanied by cellular immunity defects and genetic variants capable of driving the clinical picture toward CVID. It must be emphasized that IgG2 deficiency, which plays a vital role in the defense against encapsulated bacteria, significantly increases the risk of recurrent LRTIs.

Our prospective findings demonstrate that regular IgRT plays an "equalizing" role, independent of patients' baseline immunological phenotypes and disadvantages; by alleviating the infection burden, it significantly improves the health-related quality of life of children. However, despite the high satisfaction with the clinical success of IgRT in preventing symptoms, the practical difficulties of chronic intravenous administration limit the global treatment satisfaction of patients. This finding suggests that alternatives that reduce hospital dependency, such as SCIG therapy, should be considered more frequently in clinical practice. In conclusion, in modern pediatric immunology practice, it is of paramount importance to shape the management of antibody deficiencies through a holistic approach that incorporates molecular genetic analyses and multidimensional PROMs, rather than relying solely on laboratory parameters.

Declarations

Competing Interests

The authors have no conflicts of interest to declare.

Ethics Approval and Consent to Participate

This study protocol was reviewed and approved by the Sakarya University Faculty of Medicine Ethics Committee (approval number E-43012747-050.04-51317-471, date 20.09.2025). Written informed consent was obtained from the parents/legal guardians of all participants prior to enrollment.

Consent for Publication

Not applicable. This manuscript does not contain any individual person's identifiable data, images, or videos.

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Author Contribution

L.K. (Lütfi Kılınçkaya) contributed to conceptualization, data collection, formal analysis, and writing of the original draft. E.T.Ö. (Ece Tüsüz Önata) contributed to methodology and data collection of the manuscript. Ö.Ö. (Öner Özdemir) contributed to conceptualization, supervision, methodology, and critical revision of the manuscript. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Data Availability

The data that support the findings of this study are not publicly available due to privacy and ethical restrictions concerning pediatric patient information but are available from the corresponding author (Ö.Ö.) upon reasonable request.

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Figures

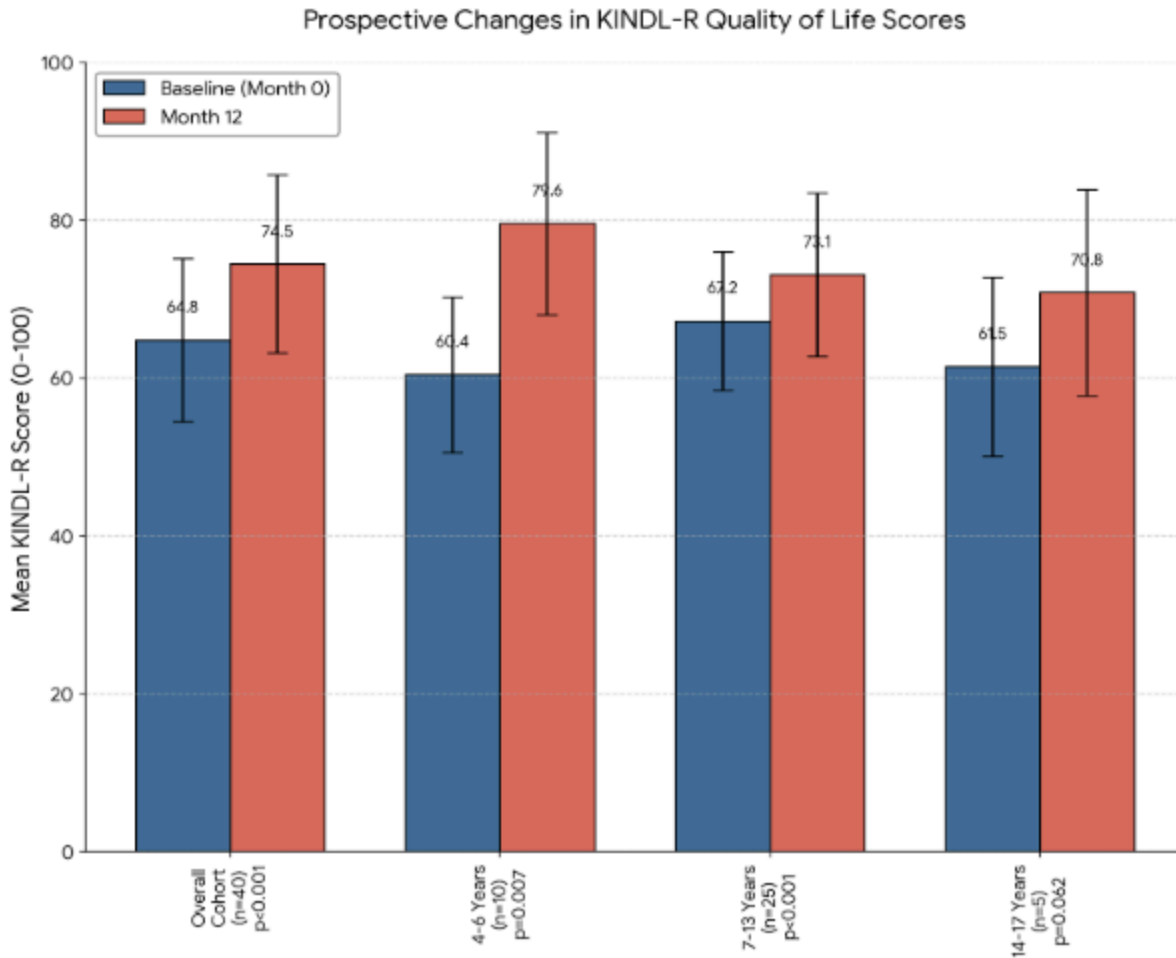


Figure 1

Prospective changes in KINDL-R health-related quality of life scores from baseline (Month 0) to Month 12, stratified by age groups. All KINDL-R scores were transformed to a standardized 0–100 scale, with higher scores reflecting a better health-related quality of life. Statistical significance for pre- and post-treatment comparisons was determined using the Wilcoxon Signed-Rank Test. Bold values indicate statistical significance ($p<0.05$). Error bars represent standard deviations.

TSQM-9 Treatment Satisfaction Profile

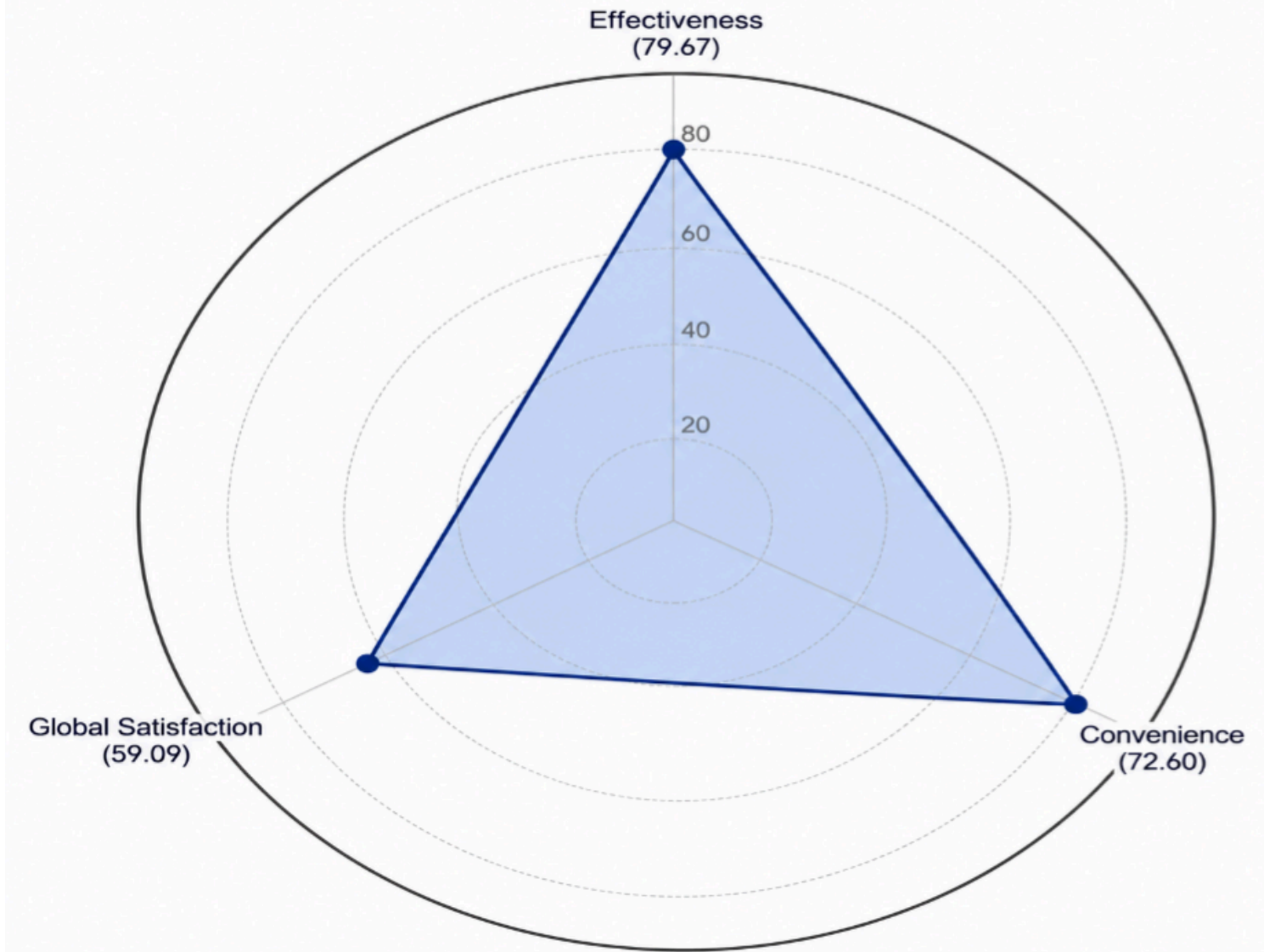


Figure 2

TSQM-9 treatment satisfaction profile of pediatric patients after 12 months of immunoglobulin replacement therapy (IgRT). The radar chart displays mean scores for the three domains of the questionnaire: Effectiveness (79.67), Convenience (72.60), and Global Satisfaction (59.09). All scores were standardized to a 0–100 scale, with higher scores indicating greater satisfaction in each respective domain.