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ORIGINAL ARTICLE

Quality of Life of Patients with Wiskott Aldrich Syndrome and X-Linked Thrombocytopenia: a Study of the Primary Immune Deficiency Consortium (PIDTC), Immune Deficiency Foundation, and the Wiskott-Aldrich Foundation

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Abstract

Background We undertook a study to determine the impact of Wiskott Aldrich Syndrome (WAS) and X-linked thrombocytopenia (XLT) and their therapies upon the health-related quality of life (HRQOL) of patients and their families.

Materials and Methods We undertook a survey of patients and their families, who self-identified as having either WAS or XLT. We assessed the PedsQL™ 4.0, the parent proxy form, and the family impact module. These results were compared with normative data from previously published reports.

Results Sixty-eight patients (29 patients completed both the PedsQL™ 4.0 and the parent proxy form; 21 completed only the PedsQL™ 4.0; and 18 completed only the parent proxy form) were included. In contrast to patient-reported outcomes, parents of patients who had a bone marrow transplant (BMT) reported that their children had better QOL scores compared with those who did not (82.6 vs. 73.3, $p = 0.023$). The QOL of patients vs. previously published normative data showed decreases in patient scores for psychosocial health (72.62 vs. 86.58, $p = < 0.001$), emotional functioning (69.91 vs. 82.64, $p = < 0.001$), social functioning (77.55 vs. 91.56, $p = < 0.001$), and school functioning (70.46 vs. 85.67, $p = < 0.001$). The family impact study revealed deficits in emotional, social, and cognitive functioning, communication, and worry.

Conclusion These results show that patients with WAS/XLT are significantly impacted with respect to QOL. BMT offered a better QOL for patients according to parents, but not as reported by the patients. Future studies should incorporate QOL to provide more data and a better understanding of outcomes for long-term survivors and decision-making regarding BMT.

Keywords Wiskott Aldrich Syndrome (WAS) · X-linked thrombocytopenia (XLT) · bone marrow transplant (BMT) · quality of life (QOL)

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Background

Wiskott Aldrich Syndrome (WAS) is a severe X-linked recessive immune disorder which is caused by a mutation in the *WAS* gene. A mutation in the *WAS* gene results in a variety of clinical manifestations ranging from the milder X-linked thrombocytopenia (XLT) to the classic WAS phenotype, which is characterized by micro-thrombocytopenia, immunodeficiency, eczema, and susceptibility to lymphoproliferative tumors and autoimmune disorders [1–3].

The estimated incidence of WAS is 1–4 cases per million live births with an average age at diagnosis of 24 months [4]. The estimated prevalence of WAS is 1.2% of patients with identified primary immune deficiencies [4].

Allogeneic bone marrow transplant (BMT) is a curative option for this disorder. Excellent outcomes exist for patients undergoing BMT with survival rates > 95% [5–8]. For patients receiving an alternative donor transplant after year 2000, the 5-year survival rate has been > 90%, showing the steady improvement of survival over time [7, 9]. With the increasing survival rates for this disease, health-related quality of life (HRQOL) is becoming more important, given that long-term patient survival may require care due to chronic illnesses, such as GVHD, autoimmunity, risk of infections, delays in growth and development, and possibly secondary neoplasms.

Chronic illness refers "to diseases with a protracted course for which treatment may be associated with long-term complications" [10]. Caring for a child with a chronic illness can have a significant impact upon patients, parents, and other family members. Most families with children with chronic illnesses have additional demands compared with those who do not (financial, worry about the future, dealing with a complicated health care system, marital strain, and conflict and guilt of passing on a "bad gene"). Some families are able to cope with these stressors better than others.

There have been several studies assessing the impact of caring for children with a variety of chronic illnesses using the Pediatric Quality of Life Inventory™ Version 4.0 (PedsQL™ 4.0) and the PedsQL™ Family Impact Scale. Studies which have utilized the PedsQL include diseases such as asthma, pediatric cancer, complex heart disease, cerebral palsy, diabetes, end-stage renal disease, pediatric GI disorders, obesity, and juvenile rheumatoid arthritis [11]. Barlogis et al. evaluated patients in France with primary immune deficiencies and reported that 40% of those patients had at least one grade 4 chronic condition and 83% had a grade 3 or 4 chronic condition [12].

In collaboration with the Wiskott-Aldrich Foundation, Immune Deficiency Foundation, Israeli Wiskott-Aldrich Foundation, and the Primary Immune Deficiency Treatment Consortium (PIDTC, an NIH-funded rare disease consortium), we undertook a study to identify the impact of WAS and XLT and its therapies upon patients and the burden it imposed upon family members. Although new therapies such as gene therapy are being developed, the only curative therapy for WAS at this time is an allogeneic BMT. We hypothesized that those patients who received a BMT would have different QOL compared with those who did not. In addition, we also evaluated the parent's well-being and their proxy report of their child's health quality of life (HRQL) and compared this with previously published studies in children with no identified chronic disease.

Materials and Methods

After obtaining approval from the Schulman IRB (now Advarra), parents and patients were invited to participate in the survey through direct mailings to email addresses from the patient databases of the Immune Deficiency Foundation, the Wiskott-Aldrich Foundation, and the Israeli Wiskott-Aldrich Foundation. In addition to 160 directly solicited participants, additional subjects were able to access the survey instrument through the websites of the sponsoring patient advocacy groups. The patients and families responded anonymously to the study by giving electronic consent. The survey was opened on March 25, 2015, and collected data through April 25, 2015. Of the respondents, 42 were reported being from an international site and the remainder were from the USA.

Subject Population

A total of 68 patients responded to the initial request to participate in this study. Of these, 68 patients: 29 patients (who were between the ages of 5 and 21) completed both the PedsQL™ 4.0 and their caregivers completed the parent proxy form; 21 patients (who were between the ages of 5 and 21) completed only the PedsQL™ 4.0; and 18 patients (who were less than 5 years of age) had only their caregiver complete the parent proxy form.

A medical and demographic questionnaire was designed by the authors for the purposes of gathering general background information about the patient and the family participants and details of disease sequelae and treatments. Data elements included basic demographics, date of onset of symptoms and date of diagnosis, lifetime and recent clinical sequelae of infection, bleeding and immune dysregulation, and current and recent history of treatment with supportive care (antibiotics, immunoglobulin replacement, transfusions, immunomodulatory drugs, splenectomy), or definitive therapy (allogeneic BMT). A summary of patient characteristics is shown in Table 1. Some of this information was used descriptively only and other information was used for data analysis. Separate versions of the questionnaire were developed for parents of minor patients and for adult patients.

Table 1 Demographics

	Yes	No
Age at diagnosis	8 months (0–216 months)	
Presence of BMT	32 (47.1%)	36 (52.9%)
Presence of cGVHD	5 (15.6%)	27 (84.4%)
Perceived presence of a chronic health condition	25 (36.8%)	43 (63.2%)
History of autoimmunity	35 (51.5%)	30 (44.1%)
ER visits in the previous year	31 (45.6%)	37 (54.4%)
History of autoimmunity	35 ((51.5%)	30 (44.1%)
History of bleeding in the previous year	39 (57.4%)	29 (42.6%)
History of environmental allergy in the past 2 years	39 (57.4%)	27 (39.7%)
History of infection in the past 2 years	50 (73.5%)	18 (26.5%)
Splenectomy	14 (20.6%)	54 (79.4%)
Treatment with IVIG in the past 2 years	48 (70.6%)	18 (26.5%)

Measures

The Pediatric Quality of Life Inventory™ Version 4.0

The 23-item PedsQL™ 4.0 Generic Core Scales encompass: (1) Physical Functioning (8 items), (2) Emotional Functioning (5 items), (3) Social Functioning (5 items), and (4) School functioning (5 items). The instrument is self-reported by patients or caregivers and takes approximately 5–10 min to complete. This scale has been extensively studied and validated in a variety of patient populations as well as in children with no identified illness between the ages of 2–18 [13, 14]. Each form requires patients to rate their problems during the past month with physical functioning (e.g., "doing chores around the house"); emotional functioning (e.g., "feeling sad or blue"); social functioning (e.g., keeping up with playing with other children"); and school functioning (e.g., missing school because of not feeling well"). Mean scores are calculated based on a 5-point Likert scale for each item and transformed to a 0 to 100 scale with a higher score representing better quality of life. Patients greater than 5 years of age completed the PedsQL™ 4.0. The healthy children sample was derived from the initial field test described by Varni et al. [15].

PedsQL Parent Proxy Report

Although pediatric self-reporting is the standard for measuring quality of life, there are circumstances in which the child is too young or cognitively impaired and cannot answer the questions. Therefore, a parent proxy report was developed and validated [16]. The PedsQL Proxy Report requires parents to respond to 20 items related to the child's quality of life. Patients less than 5 years of age had only a parent proxy form and parents of children between 5 and 21 years of age had both the PedsQL and the parent proxy form.

PedsQL Family Impact Module

The PedsQL Family Impact Module [17] is a self-report questionnaire that consists of 36 items and assesses how much of an impact a child's chronic health condition has had on the parents and family during the past month. Items measure a parent's difficulties in 8 scales: physical functioning, emotional functioning, social functioning, cognitive functioning, communication, and worry (e.g., "I feel that others do not understand my family situation"). There are also two scales that address problems specific to the family's daily activities and family relationships (i.e., stress or tension between family members). A 5-point Likert scale is used to evaluate the frequency of the child's reported experiences for each item which is then transformed to a 0 to 100 scale, with higher scores denoting a better family functioning.

The Family Impact Module yields 3 summary scores: total score, parental health-related quality of life summary score, and family functioning score. The total score is comprised of the average of the responses to all items in the questionnaire. Responses to the family impact module were scored to provide a total family impact score as well as subscores for physical, emotional, social, and cognitive function as well as communication, worry, daily activities, and family relations. Responses to the family impact module were compared with normative data previously published [18].

The various modules were implemented in an interactive, adaptive online format hosted by Qualtrics^{xm} Data were stored in a proprietary database by Qualtrics^{xm}. Responses to the PedsQL™ were scored using the PedsQL scoring manual. The Family Functioning Summary Score (8 items) is computed as the sum of the items divided by the number of items answered (which accounts for missing data). This computation is consistent with previously published PedsQL™ peer-reviewed publications and other well-established HRQOL measures [19, 20].

Statistics

Descriptive statistics (median and range for continuous variables, frequencies/percents for categorical variables) were summarized by disease group, and compared between disease groups using Kruskal-Wallis tests or chi-square tests as appropriate. QOL scores were summarized for each domain and for summary scores using mean and SD. Relevant comparisons between clinical groups of interest were done in univariate analysis using the two-sample *t* test or analysis of variance. Stepwise model building was used with a significance level of 0.05 to identify variables included in the model. Comparisons of parent and child QOL assessments to normative controls were also done using the two-sample *t* test from the available summary data.

Results

Demographics

A total of 68 patients and 47 caregivers participated in this study. Patients/parents self-identified as either having XLT ($n = 17$) or WAS ($n = 51$). The patient age at diagnosis ranged from 0 to 216 months, with a median age of 8 months. Due to the X-linked nature of this disease, all patients were male. We evaluated the patient and parent responses for QOL and analyzed the data to see differences based on the following parameters that were assessed: (1) XLT vs. WAS, (2) presence of a bone marrow transplant (BMT), (3) BMT donor type, (4) presence of cGVHD, (5) perceived presence of a chronic health condition, (6) history of autoimmunity, (7) history of an ER visit in the past year, (8) history of bleeding episode in the past year, (9) history of an environmental allergen in the past 2 years, (10) history of an infection in the past 2 years, (11) splenectomy, and (12) treatment with IVIG in the past 2 years (Table 1).

Patient and Parent Proxy QOL

There were no significant differences in the QOL scores for patients who self-identified as either XLT (75.9 ± 14.54) or WAS (78.48 ± 18.14) $p = 0.623$. The patient and parent proxy overall total QOL scores are shown in Tables 2 (patient scores) and 3 (parent proxy scores). In this study, there were no significant differences in the QOL scores in the patient-reported outcomes for any of the parameters that were assessed. In contrast, in the parent proxy-reported QOL outcomes, there were significant differences seen in those whose child had received a BMT (82.6 (BMT) vs. 73.3 (no-BMT), $p = 0.023$), ER visits in the previous year (83.8 (no ER visit) vs. 72.3(ER visits), $p = 0.004$), and a history of bleeding in the past year (83.1(no bleeding) vs. 73.5 (bleeding), $p = 0.018$). This shows that the parents perceived that the children, who received a BMT, had a better QOL post-BMT. In addition, those parents, whose children needed to visit the ER or had a history of bleeding during the previous 2 years, had a worse QOL compared with those in which these variables were not present.

QOL of Patients Who Received a BMT

Parents reported a better QOL in patients who had BMT compared with patients who had not received BMT. As a result, we decided to further evaluate these patients who received a BMT (Table 4). Of the 68 patients, 32 (47.1%) received a BMT and 36 did not. Of the patients who received a BMT, 29 stated that they had a diagnosis of WAS and 3 stated that

Table 2 Patient-related QOL scores

	Yes	No	*p* value
Presence of a BMT	81.4 (16.5)	74.9 (16.3)	0.171
Matched sibling	79.9 (19.8)		0.897
Unrelated cord blood	82.6 (5.6)		
Matched unrelated	83.7 (16.9)		
Presence of cGVHD	82.1 (14.9)	81.2 (17.2)	0.929
Perceived presence of a chronic health condition	71.9 (16.7)	81 (15.8)	0.062
History of autoimmunity	74.2 (17.9)	82.1 (14.8)	0.105
ER visits in the previous year	73.2 (17.5)	80.3 (15.7)	0.146
History of bleeding in the previous year	77.1 (17)	78.6 (16.3)	0.755
History of Environmental allergy in the past 2 years	74.4 (16.7)	83.6 (15)	0.058
History of infection in the past 2 years	78 (16.5)	76.9 (17.4)	0.835
Splenectomy	73.1 (16.8)	79.5 (16.3)	0.222
Treatment with IVIG in the past 2 years	74.4 (16.8)	83 (14.7)	0.092

Table 3 Parent proxy-reported QOL scores

	Yes	No	*p* value
Presence of a BMT	82.6 (12.8)	73.3 (14.2)	0.023
Matched sibling	84.1 (11.6)		0.590
Unrelated cord blood	80.1 (6.8)		
Matched unrelated	86.5 (12.9)		
Presence of cGVHD	82.2 (11.6)	82.6 (13.3)	0.951
Perceived presence of a chronic health condition	78.1 (16.7)	78.6(15.1)	0.917
History of autoimmunity	77.4 (12.5)	80.1 (16.3)	0.527
ER visits in the previous year	72.3 (13.9)	83.8 (12.1)	0.004
History of bleeding in the previous year	73.5 (14.1)	83.1 (12.1)	0.018
History of environmental allergy in the past 2 years	77.3 (15.2)	79.3 (12.8)	0.642
History of infection in the past 2 years	77.5 (15.1)	80 (12.3)	0.558
Splenectomy	70.1 (10.1)	79.2 (14.2)	0.220
Treatment with IVIG in the past 2 years	77 (14.7)	79.9 (11.4)	0.560

they had XLT. The year of transplant ranged from 1977 to 2011 (median 2006). The patients, who completed the QOL themselves, were all > 5 years of age, whereas the parent proxy forms were completed by the parents of those who were < 18 years of age. Of the 32 patients who received a BMT, 7 felt that they had a chronic health condition and 25 did not. Of these 32 BMT recipients, 27 of them had received IVIG in the previous 2 years.

Generic Core Scales Comparing WAS vs. Normal Subjects

The generic core scales of QOL measure the physical and psychosocial health as well as the emotional, social, and school functioning. The results from our subject group are shown in Table 5 and compared with those previously published, healthy normative subjects [15]. In this analysis, patients were compared with normal subjects who had no health issues. The patient self-reported score was 77.73 vs. normal subjects 87.61, $p = <0.001$. The parent proxy reports were similar to those self-reported patient scores (77.53 (patient) vs. 83 (healthy subjects), $p = 0.01$).

Both patients and parents reported similarly decreased scores compared with children without identified chronic illnesses in most areas except emotional health. Patients who responded to this survey had significantly lower QOL scores compared with subjects without identified chronic illness for psychosocial health (72.62 vs. 86.58, $p = <0.001$), emotional functioning (69.91 vs. 82.64, $p = <0.001$), social functioning (77.55 vs. 91.56, $p = <0.001$), and school functioning (70.46 vs. 85.67, $p = < 0.001$) but not physical health. Therefore, the outward appearance may not be different from normal children, but the emotional and social health, which are internal feelings, were lower.

Similar to the patient responses, the parents reported that their children had significant decreases in QOL in the areas of psychosocial health (73.3 vs. 82.38, $p = < 0.001$), social functioning (79.26 vs. 87.42, $p = 0.00$ and school functioning (70.94 vs. 78.46, $p = 0.043$). However, the parents did not perceive a difference in emotional functioning.

Table 4 Patients who received a bone marrow transplant

	No	Yes	*p* value
Perceived presence of a chronic health condition	25	7	0.016
History of autoimmunity in the past 2 years	14	16	0.94
History of bleeding in the past 2 years	15	17	0.5
History of IVIG in the past 2 years	4	27	0.013

Family Impact Analysis

The results of the family impact analysis are shown in Table 6. This analysis evaluates the impact of this disease upon the entire family instead of the patients themselves. Results are shown in comparison with previously published normative data [18]. Using a standard score of 100, the patients' families had lower scores compared with families of healthy controls in the areas of emotional function (median 68.1), social function (median 70.2), communication (median 63.5), and worry (median 53.7). These scores are suggestive of decreased emotional and social functioning and increase problems of communication and worry among the family members compared with those who did not have a child with a chronic illness. There was a wide range of scores on this analysis; therefore, we could not calculate the significance of these results.

Discussion

We aimed to assess the quality of life for patients with WAS or XLT and the impact that this disease has upon

Table 5 PedsQL Generic Parent/Patient Report: comparison with healthy normative sample

	Normative data of healthy subjects [15]	Patient self -reported score	*p* values	Normative data of healthy subject parent report [15]	Parent reported score	*p* values
Scale	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
N	717	54		400	54	
Total score	87.61 (12.33)	77.73 (17.06)	< .001	83 (14.79)	77.53 (14.64)	0.011
Physical health	87.53 (13.5)	87.27 (17.37)	0.894	84.41 (17.26)	85.14 (14.55, *n* = 53)	0.769
Psychosocial health	86.58 (12.79)	72.62 (21.57)	< .001	82.38(15.51)	73.33 (16.99)	< .001
Emotional functioning	82.64 (17.54)	69.91 (26.14)	< .001	80.86 (19.64)	84.62 (15.07)	0.177
Social functioning	91.56 (14.2)	77.55 (21.71)	< .001	87.42 (17.18)	79.26 (19.07)	0.001
School functioning	85.47 (17.61)	70.46 (26.30)	< .001	78.63 (20.53)	70.94 (21.53, *n* = 32)	0.043

Higher scores indicate better functioning on a scale of 1–100

the whole family. This study is the largest study of QOL in primary immune disorders reported to date. Although the numbers of patients is limited, there is much useful information that this study provided regarding the QOL and the impact on the patients and families that completed these questionnaires.

Parents are often used as surrogates to ascertain a measure of their child's QOL. However, it is not unusual for parents and children to have different opinions of their health status. Imperfect responses have long been reported between patient self-report and parent proxy reports [21]. The differences in responses are often true for areas of internal feelings (sadness, pain, fatigue, and gastrointestinal symptoms) rather than external symptoms such as aggression, school behavior, and hyperactivity). Areas of internal feelings are reflected more in patient scores, whereas external symptoms are reflected in parent scores. In our study, parents reported lower QOL scores for two specific areas (emergency room visit in the previous year and a history of bleeding in the previous year). Both of these parameters are external and the parents can see that their child needs an intervention. This suggests that these children may have had more external symptoms that the parents could see. It is interesting to note that the patients did not feel they had any difference in their physical health compared with their peers. However, they had significant differences in their emotional functioning. This was in contrast to the parents who did not perceive their children having deficits in their emotional functioning. This is an interesting point as the parents may not fully appreciate the emotional burden of this disease on their child.

Table 6 Family impact analysis

	Patient average scores (SD) *N* = 28	Patient median score (Range)	Healthy control median [16]
Physical function	72.3 (28.83)	Median 87.5 (0–100)	70.8 (54.2–91.7)
Emotional function	68.1 (27.48)	Median 65 (20–100)	75 (60–100)
Social function	70.2 (30.09)	Median 81.25 (0–100)	81.3 ((60.9–100)
Cognitive function	73.4 (28.63)	Median 90 (5–100)	75 (53.8–96.3)
Communication	63.5 (28.74)	Median 75 (8.3–100)	91.7 (75–100)
Worry	53.7 (29.20)	Median 65 (10–100)	80 (52.5–100)
Daily activity	75.2 (28.47)	Median 100 (0–100)	75 (50–100)
Family relations	76.6 (23.94)	Median 100 (0–100)	87.5 (65–100)

Parents of children who received a BMT (regardless of stem cell source) reported a significantly better QOL for the patient compared with those who did not receive a BMT. This is presumably because the BMT survivors are cured of their primary disease and therefore have fewer/no bleeding episodes and ER visits. In addition, the parents have the perspective that their child is alive, despite any complications associated with BMT. Our study yielded similar results to previous studies that showed that the QOL of patients improved following BMT for patients with other primary immune deficiency such as chronic granulomatous disease (CGD) and X-linked hyper IGM syndrome [22, 23].

Patients, unlike their parents, do not have the same perspective that their QOL is better. There are many possible reasons as to why the BMT survivors may not show a significant improvement in their QOL. The patients who completed this survey were transplanted at a young age and may not have the perspective of what their life would have been had they not received a transplant. The only perspective patients have is a comparison to their peers. Some of the other possibilities are chronic GVHD (cGVHD), other organ toxicities related to chemotherapy, and social isolation following BMT. Chronic GVHD is a rare but potentially severe complication following BMT. Depending upon the extent, cGVHD can impact a variety of organ systems and cause significant fatigue and possible pain. Patients with cGVHD are often unable to keep up with their siblings or peers. In our study, there were only 5 patients who stated that they had chronic GVHD; therefore, we are unable to determine whether this would contribute to the QOL of those who received a transplant for WAS. Specific questions related to organ toxicities post-BMT were also not asked in this study to determine if that contributed to the QOL of these patients.

The PedsQL™ Family Impact Module demonstrated that our population of WAS/XLT patients and their families may experience more worry and difficulty with communication surrounding issues related to their child's health. Previous studies utilizing the Family Impact Module for other diseases have shown that there appears to be a significant difference in family functioning for those being cared for at home vs. those being cared for in the hospital. Some of the question items in the "worry" and "communication" groups include questions such as "how will my child's illness affect other family members", "how will others react to my child's condition", and "feel others do not understand my family's situation". These questions are often difficult for families who carry a genetic disease who often have guilt of passing along a disease that might affect other family members (other male siblings or nephews). Based on the results of this study and the significant "worry" among the family, possible early interventions should be considered for these families. We have not performed quality of life among the siblings of these children and that should be considered for future studies.

There are some limitations to interpreting the results of this study. First, patients were solicited through foundation websites. As a result, the low *N* limits the generalizability to the larger national WAS population. We do not know the reasons for patients who did participate and for those who did not participate. For example, it is possible that the data were skewed to those who have a better QOL than those who may not or vice versa. Second, the condition of the disease was self-reported without external verification of the primary disease severity (XLT vs. WAS). This may have been a reason in which we did not see a difference in QOL between patients with XLT or WAS. Children were often too young at the time of diagnosis and may not know their accurate diagnosis. Some children were transplanted many years ago and there may or may not have been genetic diagnostic tests to confirm WAS vs. XLT. As a result, we do not know if this contributed to the lack of difference between WAS and XLT QOL scores. Third, we do not know particular aspects of the child's care and environment and if that too would have impacts on the overall QOL for these children and their families. Although the lack of some of the verifiable clinical data may be considered a limitation, the purpose of this study was to document the real life experiences of patients and families impacted by WAS. By that, it means we believe we have succeeded.

In conclusion, this study provided valuable information into an area that is often overlooked in clinical trials. Our study shows that patients with WAS, like those with other primary immunodeficiencies, continue to be impacted along with their families due to their disease and its therapies. It is important to note that the parent's perception is that the QOL is improved for those who received a BMT compared with those who did not. This perception is different between the parents and the patients. As we build future prospective trials for patients with Wiskott Aldrich Syndrome as well as other primary immunodeficiencies, assessment of patient-reported and parent-reported QOL and family impact studies should be incorporated. This will allow us to better understand the implications of our therapies and help the physicians, who care for these patients, to ultimately improve the quality of life for these children and their families. In addition, it will be imperative to follow children and families over time as the impact of chronic diseases and their therapies are constantly evolving.

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Authors' Contributions AS, MC, and BL analyzed and interpreted the data.

RS, SI, CS, CM, MHA, and MC designed the study.

BL and ZY provided statistical analysis.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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