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ORIGINAL ARTICLE

Health-Related Quality of Life of Patients and Families with Primary Immunodeficiency in Malaysia: a Cross-Sectional Study

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Abstract

Purpose Primary immunodeficiency disease (PID) affects various aspects of a patient's life. However, the health-related quality of life (HRQOL) of PID among Malaysian patients is poorly described. This study aimed to determine the quality of life of PID patients and their respective parents.

Method This cross-sectional study was performed from August 2020 to November 2020. Patients with PID and their families were invited to answer the PedsQL Malay version (4.0) questionnaire, the tool used to assess the HRQOL. A total of 41 families and 33 patients with PID answered the questionnaire. A comparison was performed with the previously published value of healthy Malaysian children.

Result Parents of respondents recorded a lower mean of total score than the parents of healthy children (67.26 ± 16.73 vs. 79.51 ± 11.90, p-value = 0.001, respectively). PID patients reported lower mean total score to healthy children (73.68 ± 16.38 vs. 79.51 ± 11.90, p-value = 0.04), including the psychosocial domain (71.67 ± 16.82 vs. 77.58 ± 12.63, p-value = 0.05) and school functioning (63.94 ± 20.87 vs. 80.00 ± 14.40, p-value = 0.007). No significant difference of reported HRQOL when comparing between subgroup of PID on immunoglobulin replacement therapy and those without immunoglobulin replacement (56.96 ± 23.58 vs. 65.83 ± 23.82, p-value 0.28). Socioeconomic status was found to be predictive of the lower total score of PedsQL in both parent and children reports.

Conclusion Parents and children with PID, especially those from middle socioeconomic status, have lower HRQOL and school function impairment than healthy children.

Keywords Health-related quality of life · Inborn errors of immunity · Primary immunodeficiency · PedsQL · Malaysia

Introduction

Primary immunodeficiency diseases (PID) are inherited disorders caused by defects in the immune system response and function, characterized by high susceptibility to opportunistic infection, autoimmunity, and lymphatic malignancy. In Malaysia, the frequency of PID is unknown because of the absence of a national registry for PID. However, the recent published systematic review showed that the prevalence rate of PID in Malaysia is 0.37 per 100,000 population [1]. This number is considerably low compared with PID prevalence worldwide, which reports a prevalence of 1:8,500 to 1:100,000, from symptomatic patients based on several PID registries from various countries [2].

A recent systematic review demonstrated that HRQOL was lower in PID patients than in healthy individuals or

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other chronic patients, with the emotional domains as the most affected [3]. Parents of children with severe combined immunodeficiency (SCID) in the UK reported a significantly lower quality of life than those of healthy children. They may be influenced by several factors such as SCID genotypes, immunoglobulin replacement therapy recipient, and ongoing medical issues [4, 5]. Parent and child reports showed that non-transplanted children with chronic granulomatous disease also had a lower quality of life (QOL) than healthy children, particularly in the emotional difficulties, but no significant difference was reported between the transplanted and healthy children [6]. Parents of children with Wiskott-Aldrich Syndrome (WAS) who underwent hematopoietic stem cell transplantation (HSCT) reported better QOL scores compared to parents of non-transplanted WAS patients [7]**.** Previous research has linked poor QOL to a long delay in diagnosis, a high number of infectious episodes, female gender, older age, chronic lung disease, and chronic diarrhea [8].

Home-based subcutaneous immunoglobulin (SCIg) replacement therapy has greatly improved patients' daily activities due to better school days attendance, productive working days for parents, and avoidance of emergency or unplanned medical consultations and hospital visits. In addition, patients receiving SCIg have significantly higher IgG plasma concentrations than those receiving intravenous immunoglobulin replacement therapy [9]**.**

We hypothesized that the HRQOL of Malaysian PID patients and their families is lower than that of the healthy population and may be influenced by the treatments they receive, such as immunoglobulin replacement therapy. Unfortunately, there is an absence of local data on this issue. The aim of our study is to investigate the quality of life and their associated factors, among PID patients and their families in Malaysia.

Methods

The cross-sectional study was performed from August 2020 to May 2021. Enrolled patients were those with PID diagnosis, who underwent a follow-up either at Institut Perubatan and Pergigian Termaju (IPPT), Pulau Pinang or Hospital Universiti Sains Malaysia (USM), Kelantan, and those were registered under "Persatuan Pesakit Imunodefisensi Primer Malaysia" (MyPOPI). Given the travel restriction due to the COVID-19 pandemic at the time of the study period, the participants were given an invitational link to the study information and questionnaire via personal text messaging. A total of 49 PID families were invited to participate in this study. Both parental consent and child assent were obtained prior to the study commencement. The study received approval from the Human Research Ethics Committee, USM (Ref: USM/JEPeM/20040229).

We utilized the Pediatric Quality of Life Inventory Generic Core Scale (PedsQL) version 4.0 which was readily validated in either Malay or English language [10]. The tool has been validated version in the Malay language with Cronbach's alpha coefficients of 0.86 [11]. It has a total of 23 items distributed into four domains: physical functions (8 items), emotional functions (5 items), social functions (5 items), and school functions (5 items). A 5-point Likert scale of the scoring system was used, from 0 (never) to 4 (almost always). A comparison was made with QOL scores of healthy normal children obtained from the previously published literature [9]. The socioeconomic status of the families was according to Malaysian categories of monthly household income and was categorized into 3 groups, which is B40 (earned less than USD 1058/month), M40 (earned between USD 1058/month – USD 2335/month), and T20 (earned more than USD 2335/month) [11].

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS) version 25 and STATA SE version 16. Numerical variables were checked for their distribution and presented as mean and standard deviation (median and interquartile range for skewed distribution). Categorical variables were presented as frequency and percentage. An independent *t*-test was used to compare mean PedsQL scores between variables with two groups. One-way ANOVA was employed to compare PedsQL scores between variables with more than two groups. Multiple regression analysis was performed to determine the association of risk factors and reported mean PedsQL total score. The level of significance in this study was set at 0.05 (two-tailed).

Results

A total of 41 families/parents and 33 patients with PID answered the questionnaires (response rate = 83.8%). The demographic and medical characteristics of the patients are summarized in Tables 1 and 2. The mean age of PID patients was 14.41 ± 11.24 years, and the median age of respondents was 11 years old (IQR 4–25). The majority of PID patients in this cohort aged between 7 and 12 years old (39%). Most of them were male ($n = 31$) and receiving immunoglobulin replacement therapy (IGRT, $n = 28$). The PID diagnoses were predominantly antibody deficiency ($n = 22$), particularly X-linked agammaglobulinemia, followed by combined immunodeficiencies with associated or syndromic features ($n = 6$) and congenital defects of phagocyte number, function, or both ($n = 5$).

The generic score of PedsQL version 4.0 measures the patients' physical health, psychosocial health, emotional, social, and school functioning. Results from our

Table 1 Demographics and baseline characteristics of PID patients responded to the PedsQL questionnaire

Characteristic	Frequency (%) ($N=41$)
Gender of the child/patient	
Male	31 (75.6)
Female	10 (24.4)
Parent relationship	
Mother	28 (68.3)
Father	13 (31.7)
Ethnicity	
Malay	28 (68.3)
Chinese	6 (14.6)
Indian	6 (14.6)
Sabah Bumiputera	1 (2.4)
States	
Sabah	1 (2.4)
Johor	4 (9.8)
Pulau Pinang	2 (4.9)
Perak	9 (22.0)
Kedah	3 (7.3)
Kelantan	2 (4.9)
Pahang	2 (4.9)
Terengganu	4 (9.8)
Kuala Lumpur	5 (12.2)
Selangor	9 (22.0)
Age group of the child/patient	
1–6 year	9 (22.0)
7–12 year	16 (39.0)
13–18 year	8 (19.5)
> 18 years	8 (19.5)
Welfare support	
Yes	9 (22.0)
No	32 (78.0)
Socioeconomic status	
Lower income group (B40)	21 (51.2)
Middle income group (M40)	14 (34.1)
Higher income group (T20)	6 (14.6)

subjects are shown in Table 3, and a comparison with healthy Malaysian children was performed [10]. Parents of children with PID reported significantly lower mean scores in most domains, except emotional functioning, as compared with parents of healthy children (total score, 67.26 ± 16.73 vs. 79.51 ± 11.90, p-value $= 0.001$). In addition, PID patients reported significantly lower mean scores in comparison to healthy children in total score, psychosocial and school domains (psychosocial domain: 71.67 ± 16.82 vs. 77.58 ± 12.63, p-value $= 0.05$; school domain: 63.94 ± 20.87 vs. 80.0 ± 14.40, p-value $= 0.007$).

A subgroup comparison was attempted between patients who receive and those who do not receive immunoglobulin replacement therapy (IGRT). Parents of children with IGRT reported lower school functioning scores than parents of children without IGRT. In addition, there was no significant difference between PID patients who received IGRT and those without IGRT, in all domains. We did not compare the scoring between methods of immunoglobulin replacement therapy as only one participant received subcutaneous immunoglobulin and the rest of the cohort received intravenous immunoglobulin replacement therapy. There was also no significant difference of total mean scores of parent reporting comparing all the different types of PID illness (combined immunodeficiencies with associated or syndromic features = 62.19 (15.97), predominantly antibody deficiency = 69.55 (18.43), disease of immune dysregulation = 50.23 (18.23), congenital defects of phagocyte number, function or both = 72.94 (11.64), immunodeficiencies affecting cellular and humoral immunity = 58.91 (11.93), and undefined = 76.88 (18.11), p-value = 0.39).

PID families with a M40 (middle-income group) background reported the lowest total QOL score compared to those from B40 and T20 background (58.96 ± 13.36vs. 73.48 ± 16.46vs64.87 ± 18.11, respectively, p-value = 0.03, *one-way ANOVA test). From the regression analysis, the socioeconomic background was found to be predictive risk factors of poorer mean PedsQL total score, reported by parents (Table 4). In comparison, the socioeconomic background and ethnic group were the significant predictive risk factors for poorer mean PedsQL total score reported by PID patients (Table 5).

Discussion

This study is the first in Malaysia and South East Asia aimed to assess HRQOL for patients and families with PID. HRQOL is a subjective evaluation of health status regarding physical, psychological, social functioning, and well-being. Clinicians' evaluation of HRQOL unfortunately does not fit well with ratings made by patients themselves [12]. Despite the small number of patients shared in the study, valuable information was obtained from the examination of HRQOL and the impact on the participated patients and their families. This further adds to the current body of evidence especially from the health-related QOL of PID patients and family's perspective. This is also an attempt to highlight the predicaments faced by Malaysian PID patients. Males accounted for about two-thirds of the patients as X-linked agammaglobulinemia is the most common PID diagnosis in our cohort.

Parent reports were commonly used to complement child reports. In the present study, the parent and child self-reports

Table 2 Type of PID and immunoglobulin replacement therapy

Characteristics	Frequency (%) ($N=41$)
Combined immunodeficiencies with associated or syndromic features	6 (14.6)
Predominantly antibody deficiency	22 (53.7)
Disease of immune dysregulation	2 (4.9)
Congenital defects of phagocyte number, function, or both	5 (12.2)
Immunodeficiencies affecting cellular and humoral immunity	4 (9.8)
Undefined	2 (4.9)
Immunoglobulin replacement therapy	
Yes	28 (68.3)
No	13 (31.7)

Table 3 Mean PedsqL scores for ongoing immunoglobulin vs no immunoglobulin (parent and children report)

	Malaysian healthy children [9], mean (SD)	PID cohort, mean (SD)	*P*-value*	Ongoing immunoglobulin replacement, mean (SD)	No immunoglobulin replacement, mean (SD)	*p*-value$
Parent report	$n=235$	$n=41$		$n=28$	$n=13$	
Total	79.51 (11.90)	67.26 (16.73)	0.001	67.56 (18.93)	66.41 (11.70)	0.81
Psychosocial	77.58 (12.63)	67.28 (16.58)	0.004	66.31 (17.83)	69.44 (14.55)	0.59
Physical	84.84 (13.04)	67.23 (26.89)	0.004	71.32 (26.09)	57.29 (28.40)	0.13
Emotional	69.72 (17.71)	68.05 (19.39)	0.58	66.96 (21.18)	71.67 (15.27)	0.49
Social	82.21 (15.29)	73.17 (19.06)	0.01	75.00 (20.27)	70.83 (15.78)	0.53
School	80.00 (14.40)	60.61 (24.24)	0.001	56.96 (23.58)	65.83 (23.82)	0.28
Children report	$n=235$	$n=33$		$n=25$	$n=8$	
Total	79.51 (11.90)	73.68 (16.34)	0.04	73.54 (17.99)	74.13 (10.55)	0.93
Psychosocial	77.58 (12.63)	71.67 (16.82)	0.05	71.20 (18.03)	73.12 (13.25)	0.78
Physical	84.84 (13.04)	81.72 (26.24)	0.50	82.88 (23.76)	78.13 (34.51)	0.66
Emotional	69.72 (17.71)	66.67 (24.64)	0.48	65.00 (26.61)	71.88 (17.51)	0.50
Social	82.21 (15.29)	84.39 (19.47)	0.52	84.20 (21.00)	85.00 (14.88)	0.92
School	80.00 (14.40)	63.94 (20.87)	0.007	64.40 (21.66)	62.50 (19.45)	0.82

*All mean comparisons were made against Malaysian healthy children [9] using the 1 sample *t*-test / $mean comparisons performed using independent *t*-test

showed differences, especially in the psychosocial domain, where parent and child scored inconsistently [13]. Internal feelings were reflected more in patient scores, whereas external symptoms were observed in the parent scores. The differences were noted in both parent and child reports compared with normal healthy ones. Our result was comparable with a previous study on children with SCID [4, 5].

Reports were often inconsistent between parent and child. Children with chronic illness or malignancy reported a better quality of life than their parents views [14, 15]. This was probably due to subjective weightage given by both parties. A child may only experience of his or her illness, and any attempt to alleviate the clinical context would be seen as an improvement in the QOL. However, parents may have a different idea on QOL. They probably come in the context of healthy population and perhaps have a different view on HRQOL matters. Our results also showed a significant difference between the total scores of parent and patient reports. We suspect children would consider themselves physically and socially active as good QOL, which contrasted with their parents' concern in those domains. However, the parents and patients have a similar perspective on the emotional and school domains.

Parents of children with PID reported a lower total score of QOL compared to the parents of healthy children. The former also has a lower total score for all health domains, except for emotional. This might indicate a difficult parental interpretation of their children's internal feelings. Similar results were observed in children with common variable immune deficiency, where parents recorded greater social, physical, and school limitations, supporting previous findings [9]. Our patients have reported a

Table 4 Multiple regression analysis for factors predictive of parent total score PedsQL

Variable	Coefficient	Standardized coefficient (B)	St. error	*P*-value	Confidence interval (95%)
Constant	66.61	-	10.50	0.000	45.06–88.15
Gender					
Male	Ref	-	-	-	-
Female	0.50	0.01	8.18	0.95	− 16.28–17.30
Ethnicity					
Malay	Ref	-	-	-	-
Indian	− 16.36	− 0.36	8.92	0.07	− 34.68–1.94
Chinese	6.43	0.14	8.28	0.44	− 10.55–23.43
Sabah Bumiputera	− 7.80	− 0.07	18.81	0.68	− 46.41–30.81
Agency support					
Yes	Ref	-	-	-	
No	2.49	0.06	7.70	0.74	− 13.30–18.29
Diagnosis					
Combined immunodeficiencies with associated or syndromic features	Ref	-	-	-	-
Predominantly antibody deficiency	5.00	0.15	9.23	0.59	− 13.95–23.96
Disease of immune dysregulation	− 8.26	− 0.11	14.91	0.58	− 38.85–22.33
Congenital defects of phagocyte number, function, or both	9.98	0.20	13.15	0.45	− 17.00–36.97
Immunodeficiencies affecting cellular and humoral immunity	− 2.42	0.04	11.30	0.83	− 25.62–20.76
Undefined	4.07	0.05	15.77	0.79	− 28.28–36.43
Treatment					
IGRT	Ref	-	-	-	
No IGRT	1.41	0.04	8.77	0.87	− 16.58–19.41
House income status					
Lower income group (B40)	Ref	-	-	-	-
Middle income group (M40)	− 16.07	− 0.48	7.27	0.03	− 31.01– − 1.13
Higher income group (T20)	− 11.21	− 025	10.15	0.27	− 32.04–9.61

$R^2 = 0.30$, *IGRT* immunoglobulin replacement therapy

similar total QOL score compared to their healthy peers. The only significant difference was found in the school domain when compared to the healthy individuals.

According to our findings, the various PID diagnoses had no effect on the HRQOL reporting by parents and patients. Because our study was not powered to assess this, and the number of patients was small, these findings should be interpreted with caution. Furthermore, we did not collect the data on the disease burden from our cohort. A larger study on HRQOL in 665 French PID patients found that those with a higher burden of PID diseases had lower HRQOL [16]. According to a systematic review study on HRQOL among PID patients, these patients had lower HRQOL compared to any healthy individuals or patients with chronic conditions such as diabetes mellitus and juvenile idiopathic arthritis [17]. Similar findings in HRQOL and higher fatigue scores in children and young adults with PID were also seen in a Spanish study [18].

Parents of children with IGRT recorded low school functioning compared with those of children without IGRT because the former would have missed school days from their frequent hospital visits and suffered other health-related problems. Home-based subcutaneous immunoglobulin replacement therapy has been seen to improve the total HRQOL score, reducing hospital visits and emotional implications by 75.8% [9]. Other reported benefits of SCIg include effective prevention from severe infections, pulmonary, neurological, and systematic complications, and a reduction in the financial healthcare costs for patients and their families by 20–25% compared to IVIg in the hospital facility [17, 19–21]. However, some studies suggested that emotional and psychosocial problems were related to the chronic condition of children, hence leading to school absenteeism [22, 23].

Our study highlighted lower HRQOL scores reported by the PID patients and families compared to the healthy

Table 5 Multiple regression analysis for factors predictive of children total score PedsQL

Variable	Coefficient	Standardized coefficient (B)	St. error	*P*-value	Confidence interval (95%)
Gender					
Male	Ref	-	-		-
Female	−2.93	−0.07	7.81	0.71	−19.36–13.48
Ethnicity					
Malay	Ref	-	-	-	-
Indian	−16.26	−0.35	8.06	0.05	−33.21–0.68
Chinese	9.62	0.22	7.36	0.20	−5.84–25.10
Sabah Bumiputera	−29.04	−0.30	17.38	0.11	−65.57–7.47
Agency support					
Yes	Ref	-	-	-	-
No	−7.14	−0.18	7.30	0.34	−22.50–8.20
Diagnosis					
Combined immunodeficiencies with associated or syndromic features	Ref	-	-	-	-
Predominantly antibody deficiency	6.73	0.20	8.83	0.45	−11.82–25.30
Disease of immune dysregulation	−26.51	−0.38	13.26	0.06	−54.37–1.34
Congenital defects of phagocyte number, function, or both	9.04	0.15	14.32	0.53	−21.03–39.13
Immunodeficiencies affecting cellular and humoral immunity	−37.28	−0.39	18.91	0.06	−77.02–2.44
Undefined	−28.41 10.18	−0.29 0.10	19.59 17.86	0.16 0.57	−69.58–12.75 −27.33–47.71
Treatment					
IGRT	Ref	-	-	-	-
No IGRT	18.95	0.49	11.81	0.12	−5.87–43.78
House income status					
Lower income group (B40)	Ref	-	-	-	-
Middle income group (M40)	−23.93	−0.65	7.36	0.00	−39.41–−8.44
Higher income group (T20)	−4.61	−0.10	9.87	0.64	−25.36–16.13

$R^2 = 0.64$, *IGRT* immunoglobulin replacement therapy

children. It is important to note that the socioeconomic disadvantage was predictive factors for poorer HRQOL in the Malaysian PID cohort. A substantial proportion of the population is living in poor socioeconomic conditions. Malaysia is no longer just grappling with absolute poverty but also with relative poverty, pockets of persistent poverty, the traditional rural poverty, and urban poverty as well as increasing inequalities [24]. The majority of the government's financial package is aimed at assisting with daily living expenses but not essential medical expenses, and the majority of the financial assistance provided by the local government is aimed at the lowest socioeconomic group, B40. Furthermore, because PID is a hereditary disease, the lack of coverage by the local insurance health policy exacerbates the funding problem. It is still concerning that there is uncertainty on resources to the low-income group population which has led to poor QOL in patients. We believe that financial support should be offered to all families of children affected with PID, irrespective of their socioeconomic status. In a recent systematic review, a socioeconomic disadvantage may affect the QOL in children with other chronic diseases as well, such as asthma, epilepsy, type 1 diabetes mellitus, and chronic kidney disease [25]. Children with chronic health conditions experienced enormous challenges in their future careers, and they would require government support to improve their QOL. Initiatives and supportive health policy towards those with PID should not be compounded by the disadvantaged socioeconomic status but focused towards a mitigation plan to prevent the adverse outcome of their illnesses.

One of the limitations of our study was the quantitative nature of using a structured self-report questionnaire. Participants should be allowed to submit more information on their HRQOL-related matters which may be outside the scope of the tool. The PedQL questionnaire was distributed in dual language; this was an attempt to reduce language bias. A future qualitative study would be crucial to

decipher the challenges faced by Malaysian patients with PID and their families. Another limitation of this study was that due to a lack of information, we were unable to compare HRQOL with the severity of medical health status reported by the parents or patients.

Conclusion

Children with primary immunodeficiency or PID in Malaysia have lower QOL than normal healthy children. In the Malaysian PID cohort, the most affected domain was school functioning, and socioeconomic disadvantage was a predictor of poorer HRQOL. As a result, improvements and a holistic approach in healthcare policy especially for PID governance, including financial assistance, are urgently required.

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Author Contribution RAA: conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—original draft, and writing—review and editing.

IJAH: conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, supervision, and project administration.

MNAA: methodology, validation, formal analysis, investigation, resources, data curation, writing—review and editing, and project administration.

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Data Availability The datasets analyzed for this study can be made available by request to the corresponding author at intanj@usm.my.

Code Availability There was no involvement of software application or custom code in this study.

Declarations

Ethics Approval The study received approval from the Human Research Ethics Committee, USM (Ref: USM/JEPeM/20040229).

Consent to Participate Patients and families consented to participation in this study.

Consent for Publication Patients and families consented to the publication of this study.

Conflict of Interest The authors declare no competing interests.

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