QUALITY OF LIFE ASSESSMENT FOR PATIENTS AND FAMILIES WITH PRIMARY IMMUNODEFICIENCY IN MALAYSIA

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by

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LIST OF ABBREVIATION

AD	Autosomal Dominant
AR	Autosomal Recessive
BRFSS	Behavioral Risk Factor Surveillance System
CFS	Chronic Fatigue Syndrome
CGD	Chronic Granulomatous Disease
CID	Combined Immunodeficiency Disease
CMA	Chromosomal Micro-Array
CVID	Common Variable Immunodeficiency
FBC	Full Blood Count
GOF	Gain Of Function
HLH	Hemophagocytic Lympho-Histiocytosis
HRQOL	Health-related quality of life
HSCT	Hematopoietic Stem Cell Transplantation
HUSM	Hospital Universiti Sains Malaysia
IFN	InterFeroN
IG	Immuno-Globulin
IGRT	Immuno-Globulin-Replacement Therapy

IPPT	Institut Perubatan & Pergigian Termaju
IUIS	International Union of Immunological Societies
IVIg	Intra Venous Immunoglobulin
JMF	Jeffery Modell Foundation
LPPS	Lansky's Play Performance Scale
MENA	Middle East and North Africa
MSMD	Mendelian Susceptibility to Mycobacterial Disease
NK	Natural Killer
PAD	Predominantly Antibody Deficiency
PedsQL TM	Pediatric quality of life inventory TM
PID	Primary Immunodeficiency Disease
QOL	Quality of life
SCID	Severe Combined Immunodeficiency
SCIg	Sub-cutaneous Immunoglobulin
SDQ	Stress and Difficulty Questionnaire
SF-12	Short Form – 12
SLE	Systemic Lupus Erythematosus
TMP-SMX	Trimethoprime -Sulphamethoxazole
WAS	Wiskott Aldrich Syndrome

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PENILAIAN KUALITI HIDUP PESAKIT DAN KELUARGA DENGAN KEKURANGAN IMUNITI PRIMER DI MALAYSIA

ABSTRAK

Penyakit imunodefisiensi primer (PID) mempengaruhi pelbagai aspek kehidupan pesakit. Namun demikian, data penentuan kualiti hidup pesakit PID di Malaysia adalah minimal dan terbatas. Kajian ini bertujuan untuk mengetahui kualiti hidup pesakit dan ibu bapa PID Malaysia dan terbahagi kepada dua fasa. Fasa pertama adalah kajian kuantitatif di mana penilaian kualiti hidup dilakukan dengan menggunakan boring soal selidik Bahasa Melayu PedsQL (4.0). Kajian keratan rentas ini dilakukan dari Ogos 2020 hingga November 2020. Pesakit dengan PID dan keluarga mereka dijemput untuk menjawab soal selidik versi Bahasa Melayu PedsQL (4.0), alat yang digunakan untuk menilai HRQOL. Perbandingan dilakukan dengan nilai anak-anak Malaysia yang sihat yang diterbitkan sebelumnya. Fasa kedua kajian ini melibatkan temu bual kualitatif dengan sepuluh ibu bapa melalui rakaman audio di klinik PID (hospital IPPT) dilakukan dari 1 Mac hingga 30 Mei 2021, dengan anggaran masa 30 minit dengan setiap ibu bapa. Temu ramah ditranskrip dan diterjemahkan dari bahasa Melayu ke bahasa Inggeris. Selepas itu, analisis tematik melalui ATLAS.ti versi 9 dilakukan. Sebanyak 41 keluarga dan 33 pesakit dengan PID menjawab soal selidik bagi fasa pertama kajian.Ibu bapa responden mencatat min skor keseluruhan yang lebih rendah daripada ibu bapa kanak-kanak normal yang sihat (masing-masing 67.26 ± 16.73 berbanding 79.51 ± 11.90, nilai p = 0.001). Pesakit PID melaporkan skor min keseluruhan yang lebih rendah kepada kanak-kanak sihat normal (73.68 ± 16.38 vs 79.51 ± 11.90, p-value = 0.04), termasuk domain psikososial (71.67 ± 16.82 berbanding 77.58 ± 12.63, p-value = 0.05), dan fungsi sekolah, (63.94 ± 20.87 vs 80.00

± 14.40, nilai p = 0.007). Tidak ada perbezaan yang signifikan dari HRQOL yang dilaporkan ketika membandingkan antara subkumpulan PID pada terapi penggantian imunoglobulin dan yang tanpa penggantian imunoglobulin (56.96 ± 23.58 berbanding 65.83 ± 23.82, nilai p 0.28). Status sosioekonomi didapati dapat meramalkan jumlah skor PedsQL yang lebih rendah dalam laporan ibu bapa dan anak-anak. Bagi fasa kedua kajian melibatkan temu bual data kualitatif dengan ibu bapa, analisis tematik menunjukkan lima tema utama yang hidup dengan rasa takut dan cemas dengan empat subtema (penyakit, masalah psikologi, ketakutan jangkitan, masalah warisan), sokongan kesihatan PID berjuang dengan empat subtema (sistem kesihatan PID, rawatan, diagnosis, masalah kewangan), pengetahuan dengan dua subtema (masalah pendidikan, pemahaman penyakit), kekangan sosial dengan dua subtema (hubungan, pengasingan sosial), dan mengatasi tiga subtema (penerimaan, peningkatan kesihatan anak, kebersihan emosi).Ibu bapa dan anak-anak dengan PID, terutama yang berstatus sosioekonomi pertengahan, mempunyai penurunan fungsi HRQOL dan fungsi sekolah daripada kanak-kanak yang sihat. Hidup dengan ketakutan dan kegelisahan telah dikenal pasti sebagai tema utama dari analisis tematik.

QUALITY OF LIFE ASSESSMENT FOR PATIENTS AND FAMILIES WITH PRIMARY IMMUNODEFICIENCY IN MALAYSIA

ABSTRACT

Primary immunodeficiency disease (PID) affects various aspects of a patient's life. However, the health-related quality of life (HRQOL) is poorly defined in Malaysian PID patients. Using a two-phase methodology, this study aimed to determine the quality of life of Malaysian PID patients and parents. The first phase was a quantitative study involving the assessment of the quality of life using the PedsQL Malay version (4.0) questionnaire. 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: a tool used to assess the HRQOL. The data were compared with previously published values of healthy Malaysian children. The second phase of the study involved qualitative interviews meeting with 10 parents through an audio recording at PID clinic (IPPT hospital), which was conducted from 1st of March to 30th May 2021. The interviews lasted for approximately 30 minutes with each parent, and the records were transcribed and translated from Malay to the English language. Subsequently, thematic analysis via ATLAS. ti version 9 was performed. A total of 41 families and 33 PID patients completed the questionnaire (the first phase of the study). Respondents' parents recorded a lower mean total score than those of normal healthy children (67.26±16.73 vs. 79.51±11.90, p = 0.001, respectively). PID patients reported lower mean total score to normal healthy children (73.68 ± 16.38 vs. 79.51 ± 11.90, p = 0.04), including psychosocial domain (71.67±16.82 vs. 77.58±12.63, p = 0.05), and school functioning, (63.94±20.87 vs. 80.00 ±14.40, p = 0.007). No significant difference was reported in

the 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 = 0.28). Socioeconomic status was predictive of the lower total score of PedsQL in both parent and children reports. The thematic analysis of qualitative data interviews with parents revealed five main themes: living with fear and anxiety with four subthemes (sickness, psychological issues, fear of infections, and inheritance issues), PID healthcare support struggles with four subthemes (PID health system, treatment, diagnosis, and financial issues), knowledge with two subthemes (educational issues and disease understanding), social constraint with two subthemes (relationships and social isolations), and coping with three subthemes (acceptance, child health improvement, and emotional hygiene). Parents and children with PID, especially those from middle socioeconomic status, had lower HRQOL and school function impairment than healthy children. Living with fear and anxiety was identified as a major theme in the thematic analysis..

CHAPTER ONE

INTRODUCTION

1.1 Primary Immunodeficiency Diseases (PIDs)

PIDs are a diverse category of hereditary illnesses characterised by increased vulnerability to infection, autoimmunity, and cancer due to dysfunction in several components of the adaptive and innate immune systems. These illnesses were once thought to be uncommon and rare. More than 350 single gene abnormalities have been identified as causing PIDs as a result of increased awareness and the availability of better diagnostic facilities [1]. Although they are classified as "rare diseases," their global prevalence is higher than previously realised [2]. PIDs affect around six million people worldwide, with only 27,000 to 60,000 having been diagnosed [3].

PID management and research in Malaysia are fraught with difficulties. Given the absence of a Malaysian PID national registry, it is challenging to determine the actual prevalence of PID and to define the new cases. Although thought to be rare, PID does occur in the Malaysian population and has shown an increasing trend since 1986 [4]. Nevertheless, the recently published systematic review showed the prevalence rate of PID in Malaysia is 0.37 per 100,000 population [5]. The prevalence in the general population is between 1: 500 and1:500,000 worldwide, depending on diagnostic skills and medical resources available in the country [6].

To date, there is no published literature or study on health-related quality of life (QOL) among PID patients in Malaysia. This reflects the need to determine the quality of life (QOL) and factors influencing PID patients' QOL in Malaysia. Until recently, the majority of QOL research in PID patients was conducted in North America,

Australia, the United Kingdom, and the Middle East. Given the vast disparities in culture, family dynamics, socioeconomic level, health care delivery, and infrastructure, data acquired from these countries may not be appropriate to Malaysian society, highlighting the need for more research.

PID has a substantial impact on the lives of patients, reducing their ability to work as well as their physical and social activities. [7, 8]. Delays in infection detection and treatment can also impact negatively on PID patients' health-related quality of life (HRQOL) [9]. The most commonly utilised outcome criteria in clinical studies are the survival rate and recurring illness exacerbations; nevertheless, HQQOL in PID patients has recently gained extensive interest [10].

Patient-reported outcome measures such as HRQOL are now commonly employed as one of the most significant outcomes in clinical trials, addressing concerns such as patient satisfaction, treatment compliance, and treatment preferences. Typically, patient-reported outcome measures are created to measure a certain concept in a standardised manner, providing a means of quantifying qualitative information [11].

HRQOL assessments are multimodal by nature, and they might be generic or disease-specific. A generic measure is used to assess the impact of a disease or condition, whereas a specific measure is used to assess the impact of a disease or condition. Generic measurements can be used to compare across disorders, but they typically lack the sensitivity or responsiveness required to detect minor but significant changes after an intervention or medical therapy. HRQOL measures created specifically for a condition are more reliable indicators of the positive and negative

impact of that disease and treatment compared to clinical opinion or objective symptom measurement [12].

1.1.1 Problem statement & Study rationale

To date, HRQOL studies and data on Malaysian PID patients are lacking. The social determinants that could influence the outcome of HRQOL in Malaysian PID cohorts are poorly characterised and understood. This study aims to investigate the HRQOL of Malaysian PID patients and the social determinants influencing their HRQOL. This information is important in developing potential solutions to improve their HRQOL.

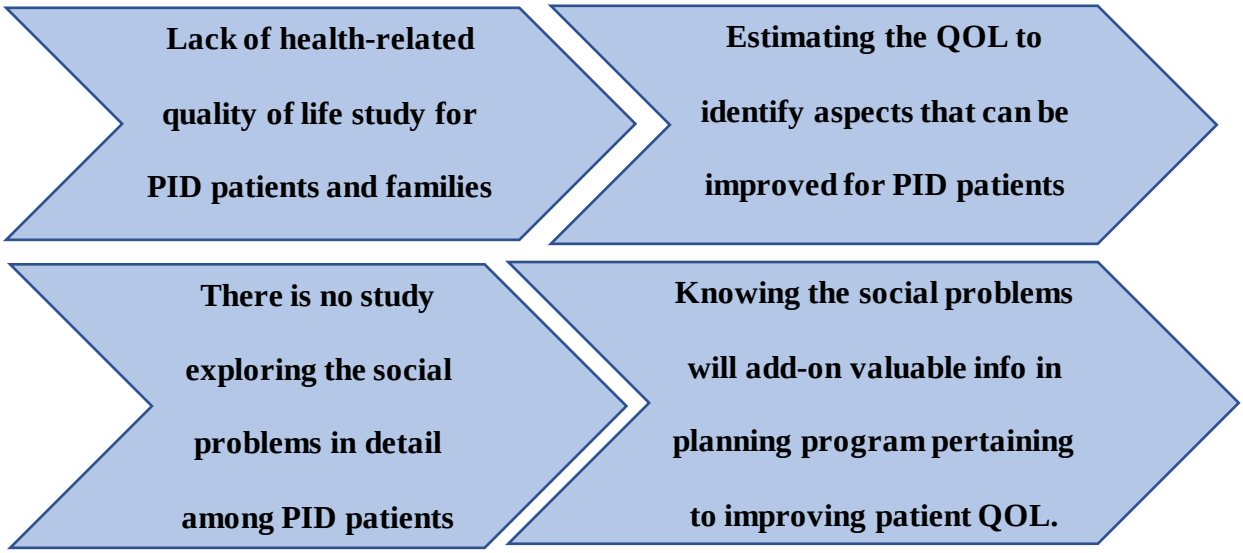

Figure 1.1: Problem statement & Study rationale

1.1.2 Conceptual framework (Theoretical framework) :

Based on previous data regarding PID children worldwide, this study hypothesised that Malaysian PID children have low QOL, notably in the social and learning components. Based on existing evidence about PID children internationally. In reaction to living and coping with their disease, children and adults may have frequent absences from school or work, restricted involvement in social and sporting activities, and a variety of psychiatric problems. Patients' preferences appeared to be for immunoglobulin treatment to be delivered in their homes, and SCIg therapy was favoured after switching from IVIg therapy [13, 14]. Several factors are expected to influence PID patients' QOL, such as total house income, ethnicity, gender, treatment, agency support and diagnosis.

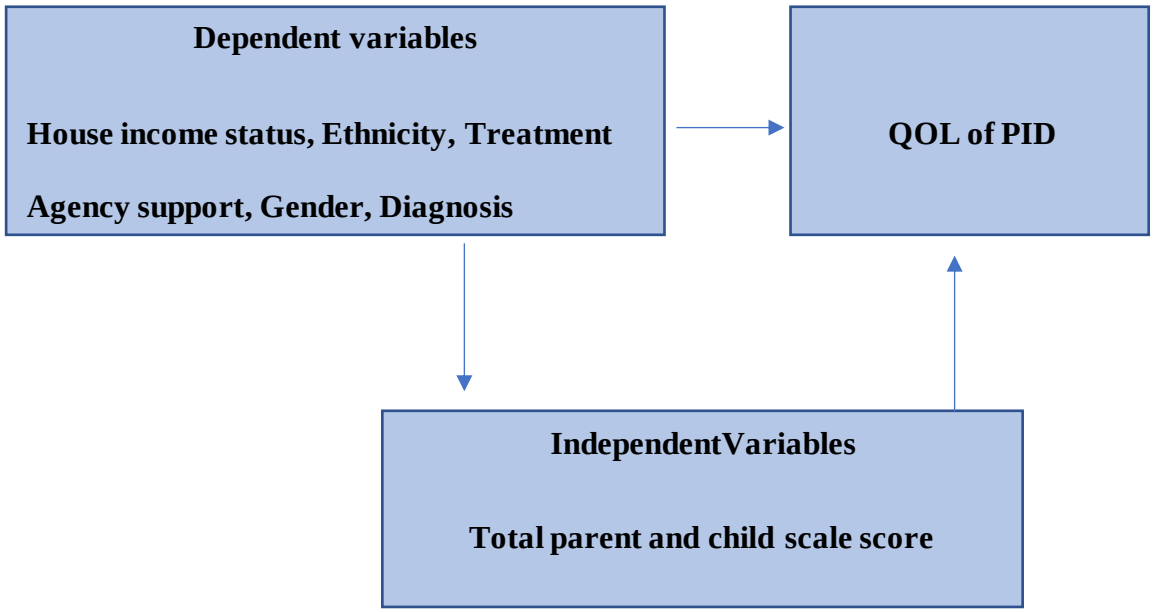

Figure 1.2: Conceptual framework (Theoretical Framework)

1.1.3 International Union of Immunological Societies (IUIS) Classification

Since the 1990s, several genetic defects have been described with advances in molecular biology. International Union of Immunological Societies (IUIS) was officially founded at a meeting in Brugge (Belgium) on May 5, 1969, by the representatives of 10 Societies, and 81 Member Societies with four regional Federations (Europe, Latin America, Africa, and Asia-Oceania), and two direct members from the USA and Canada [15]. One of the committee's objectives is to provide clinical immunologists with an update on genetic causes of immune deficiency and dysregulation every two years. The committee also provides a standardised classification that aids in uniformity in studies and reporting findings.

The International Union of Immunological Sciences was recently updated in 2020 [16]. The classification of genetic defects associated with primary immune deficiencies has increased to 430 inborn errors of immunity, including 64 novel gene defects.

1.1.3 (a) Updated Classification according to IUIS

PIDs are mainly classified into 10 categories based on IUIS classifications (2020), as mentioned in detail in Appendix A. The 10 PID forms classified under IUIS are as follows:

- **i.** Immunodeficiencies affecting cellular and humoral immunity
- **ii.** Predominantly antibody deficiencies
- **iii.** Defects in Intrinsic and Innate Immunity
- **iv.** Congenital defects of phagocyte number, function, or both
- **v.** Diseases of immune dysregulation

vi. Combined immunodeficiencies with associated or syndromic feature

vii. Complement deficiencies

viii. Autoinflammatory disorders

ix. Bone marrow failure

x. Phenocopies of inborn errors of immunity

1.1.4 Epidemiology of PID

1.1.4 (a) Worldwide

The upper estimate of PID worldwide is presently about six million people. Meanwhile, only 27,000 to 60,000 people have been recognised to date (according to all national registries and the Jeffrey Modell Centres Network) [3].

The highest projection for Europe was 638,000 cases, with 15,052 cases (2.7%) already registered [3]. According to the latest JMF global survey, about 1836 patients with PIDs were from Africa, which is a small number compared to the total population of the continent [17]. Furthermore, the estimated number of cases in Africa is estimated as 902,631 [3], while the exact prevalence of PID on the African continent remains unknown [18].

Table 1.1 Prevalence of PID according to published literature from various countries worldwide.

Name of the country	Number of Patient (years)	Prevalence/100,000	Most PID diagnosis
Europe			
Netherlands [19]	745 (2009-2012)	4.047	PAD
Poland [20]	4099 (2014)	10.6	PAD
Germany [21]	2,453	2.72	PAD (CVID)
France [22]	3,083	4.4	PAD(CVID)
United Kingdom [23]	4758	5·90	PAD(CVID)
Ireland [24]	115 (1996-2003)	1.987	PAD
Norway [25]	372 (2000)	6.82	PAD
Asia			
Japan [26]	1240	2.3	PAD
Korea [27]	N/A	1.1	PAD
Taiwan [28]	N/A	2.17	
China [29]	352 (2005-2011)	N/A	SCID
India [30]			PAD, HLH
MENA region			
Morocco [31]	421 (1998–2012)	0.81	CID
Tunisia [32]	710 (1988–2012)	4.3	CID
Egypt [33]	476 (2010–2014)	N/A	CID
Turkey [34]	1,435 (2004–2010)	30.5	PAD
Iran [35]	731 (2006–2013)	Incidence (9.7/1 million/year)	PAD

Table 1.1:Continued

Name of the country	Number of Patient (years)	Prevalence / 100,000	Most PID diagnosis
Kuwait [36]	76 (2004–2006)	11.9	PAD
Saudi Arabia [37]	504 (2010–2013)	7.2	CID
Qatar [38]	131 (1998–2012)	4.7	PAD
Oman [39]	140 (2005–2015)	7	Phagocytic disorder
USA [40], [41]	158 (1976-2006)	(Incidence 4.6 per 100,000) prevalence 126.8 (2012)	PAD
Latin America [42]	3321 (2007)	Incidence 0.72 (CGD)/ 1.28(SCID)	PAD

PAD, predominantly antibody deficiency; CVID, common variable immunodeficiency; CID, combined immunodeficiency; SCID, Severe combined immunodeficiency; CGD, chronic granulomatous disease; HLH, Hemophagocytic Lymphohistiocytosis; MENA, Middle East, and North Africa; N/A, Not Available.

1.1.4 (b) Malaysia

The estimated prevalence of PID in Malaysia is 0.37 per 100,000 population [5]. Based on IUIS classifications, Primary Antibody Defect (PAD) was the commonest class of PID, followed by phagocytic defect, combined immunodeficiencies, and other cellular immunodeficiencies, with 15% of positive family history. Among the three ethnic distributions (Malay, Indian, and Chinese), PID is mainly detected in Malays [4].

Table 1.2: The distribution of PID cases identified from the systematic review in Malaysia [5].

Class/subclass	N (%)
Immunodeficiencies affecting cellular and humoral immunity	36 (30.3%)
Severe Combined Immunodeficiency Disease	22
Combined T and B cell deficiencies	2
Hyper IgM Syndrome	7
DOCK8 deficiency	2
T cell deficiency—undefined	3
Combined immunodeficiencies with associated or syndromic features	21 (17.6%)
Wiskott–Aldrich Syndrome	10
Ataxia telangiectasia	1
Di George/velocardio-facial Syndrome	5
Hyper-IgE Syndrome	5
Predominant antibody deficiencies	24 (20.2%)
X-linked Agammaglobulinemia	17
Common variable immune deficiency	3
Selective IgA deficiency	2
CD19 deficiency	1
Undefined hypo-gammaglobulinemia	1
Disease of immune dysregulation	13 (10.9%)
Hemophagocytic Lymph histiocytosis	6
Chediak-Higashi Syndrome	3
Griscelli Syndrome (Type 2)	1
X-linked Lymphoproliferative Disorder	2
XIAP deficiency	1
Congenital defects of phagocyte number or function	20 (16.8%)
Congenital Neutropenia	6
Leukocyte Adhesion Deficiency	1
Chronic granulomatous disease	13
Defects in intrinsic and innate immunity	4 (3.4%)
IL12RB1 deficiency	1
Chronic Mucocutaneous Syndrome	3
Autoinflammatory disorders	1 (0.8%)
Autoinflammatory disorder (NLRC4 mutation)	1

1.1.5 Clinical features of PID

Children with PID have a range of presenting symptoms, which may include an infectious, autoimmune, or malignant presentation. Ten warning signs make suspicious PID according to the Jeffrey Modell Foundation (JMF) [43].

- ≥ four ear infections within one year
- ≥ two serious sinus infections within one year
- ≥ two months on antibiotics with little effect
- failure of an infant to gain weight or grow normally.
- recurrent, deep-skin, or organ abscesses
- persistent thrush in the mouth or fungal infection on the skin
- need for intravenous antibiotics to clear infections.
- ≥ two deep-seated infections including septicemia.
- family history of PID.
- presence of ≥ two of these signs may indicate PID [44].

The most prevalent symptoms were recurrent respiratory tract infection, a bacterial infection of the skin and mucous membranes, and diarrhea. In addition, 20.5% of patients experienced an adverse reaction post-vaccination [45].

A cohort-based study in Slovenia that included PID patients from the Slovenian national PID registry found that both non-infectious and non-malignant manifestations were present in 69/235 (29%) patients, including autoimmune manifestations in 52/235 (22 %), lymphoproliferative/granulomatous in 28/235 (12 %), autoinflammatory in 12/247 (5 %), and allergic manifestations in 10/235 (4 %) of all registered patients [46].

1.1.5 (a) Common patterns of infections raising the suspicion of PIDs

The most common infections of PID are; recurrent sinopulmonary infections, cutaneous or soft tissue abscess/fistula. chronic diarrhea, mucocutaneous candidiasis, severe or long-lasting warts, and generalised molluscum contagiosum. PID patients may be presented with invasive infections such as meningitis, osteomyelitis, deep organ abscess, bacteremia; or being infected with opportunistic pathogens such as *Pneumocystis jiroveci, Cryptosporidium sp., non-tuberculous mycobacteria,* disseminated varicella or recurrent herpes zoster, and systemic fungal infection (candidemia or invasive aspergillosis). PID patients may also be presented with complications of live vaccines, e.g. BCG, oral polio, rotavirus, varicella.

A full clinical history, which includes a family history of PID, consanguinity, or early neonatal death in the family relatives, coupled with a thorough physical examination and blood tests can help to diagnose several PIDs. The physical examination should be thorough and cover all body systems, including the patient's nutritional state, as well as the height and weight measurements, and any previous infection-related complications.

The presence or absence of lymphadenopathies, nodal chains, tonsils, and hepatosplenomegaly must all be assessed, as these criteria may point the healthcare professional in the direction of a specific PID. A full blood count (FBC) with a differential count might reveal cytopenia (neutropenia, monocytopenia, lymphopenia, or thrombocytopenia).

Table 1.3: Clinical features in PID subclasses [47]

Subclass	Most common presentation
T-cell and combined immunodeficiencies	SCID usually presents within the first year of life with chronic diarrhea and failure to thrive; severe, recurrent infections with opportunistic pathogens (e.g., Candida albicans [thrush], Pneumocystis jiroveci, or cytomegalovirus); and skin rashes.
B-cell immunodeficiencies	increased susceptibility to respiratory tract infections with bacteria, particularly Streptococcus pneumoniae and Haemophilus influenzas.
Innate immunodeficiencies	present at any age, often with unusual or difficult to eradicate infections. typical signs and symptoms of phagocyte disorders are severe pyogenic (pus-like) bacterial and fungal infections of the skin.
Disorders of immune dysregulation	autoimmune disease due to the dysregulation of the immune system as a whole.

The first step in evaluating humoral immunity is to check serum immunoglobulin (Ig) levels (IgG, IgM, IgA, and IgE), which might assist in the diagnosis or at least raise suspicion of quantitative Ig deficiencies, such as congenital agammaglobulinemia, CVID, or selective IgA deficiency. Other humoral changes associated with other defects like hyper-IgE or hyper-IgM syndrome might also be suspected [48].

1.1.6 Laboratory investigations

1.1.6 (a) Flow cytometry

Flow cytometry is an optical, laser-based technique for analysing the physical and fluorescence features of cells in suspension as they flow through the instrument in real-time. Direct and indirect immunofluorescent labelling of surface and intracellular

proteins expressed by lymphoid cells isolated from tissues or blood is used to diagnose PID. Both components contain critical information about antibody selection and titration, fluorochrome selection, spectrum overlap and adjustment, control usage, data synthesis, and analysis standards [49].

1.1.6 (b) Genetic test

The ability to determine the proper underlying molecular diagnosis has a direct impact on PID prognosis and is a critical guide for precise care and counselling of the affected patient and family. Since the first established genetic testing for PID in 1993, the diagnosis has become easier due to the discovery of several genes known to cause immunodeficiency and immune dysregulation disorders. Targeted and semi-targeted sequencing of candidate genes suspected of causing the patient's clinical presentation can be performed. Whole-exome sequencing, whole-genome sequencing, and next-generation sequencing panels that cover either subsets or all known therapeutically important genes are some of these options [50].

1.1.7 Treatment for PID

1.1.7 (a) Immunoglobulin replacement therapy (IGRT)

IGRT has significantly improved the prognosis of PID patients, and it is now required in those who have impaired B cell function and antibody production, such as X-linked Agammaglobulinemia and CVID [51]. CVID mortality has decreased from 29% in 1971 (before intravenous Ig was introduced) to 19.6% in 2012 with adequate immunoglobulin replacement therapy [52]. IGRT has reduced the number of bacterial pneumonia cases by half, however, it does not seem to help with other recurrent respiratory illnesses [53].

There are six PID phenotypes for which IGRT is currently recommended [54]:

1. Agammaglobulinemia due to the absence of B cells.
2. Hypogammaglobulinemia with impaired specific antibody production.
3. Selective antibody deficiencies (IGRT use must be individually evaluated).
4. Hypogammaglobulinemia with normal-quality antibody response.
5. Isolated deficiency of an IgG subclass with recurrent infections.
6. Recurrent infections due to an unknown immune mechanism.

Since the initial introduction of IgG in the 1980s, the dose of IgG has been frequently raised to attain larger IgG plasma concentrations [55]. IgG plasma concentrations to prevent bacterial infections in people with CVID can range from 5 to 17 g/L, while trough IgG levels of approximately 8 to 10 g/L are frequently advised. These values can be achieved with a dosing range of 0.2 to 1.2 g/kg/month. Patients with bronchiectasis and those with specific phenotypes may require greater doses, which must be individually adjusted [55]. There are two routes for immunoglobulin administration, namely, IgG subcutaneous (SCIG) and intravenous (IVIG). SCIG demonstrated better serum immunoglobulin bioavailability and allows home infusions compared to intravenous administration [56]. Meanwhile, physiological IgG concentrations are achieved by administering enough dosages via both methods. [57, 58]. Despite the differences in kinetics, the intravenous injection causes a rapid increase in IgG plasma concentrations, whereas subcutaneous delivery causes more gradual increases in plasma levels and more stable serum concentrations [57, 59].

Since higher mean serum levels can be achieved with lower immunoglobulin doses, SCIG can be beneficial, especially in individuals who have low IgG concentrations despite intravenous treatment [60, 61].

Both methods of administration are considered equivalent in terms of efficacy and safety [54, 62, 63]. A comprehensive evaluation of 25 studies found that patients who transitioned from hospital-administered IVIG to home-administered SCIG had a higher HRQOL [62]. SCIG therapy was also reported to be more cost-effective owing to the fewer days missed from school or job [62].

1.1.7 (b) Prophylaxis antibiotics

Trimethoprim-sulfamethoxazole (TMP-SMX) is commonly prescribed as antibiotic prophylaxis for PID patients. It prevents opportunistic infections with *Pneumocystis jirovecci* that are associated with high morbidity and mortality. Prophylactic antibiotics usage has been shown to improve PID survival outcomes [64].

1.1.7 (c) Targeted therapy of primary immunodeficiency

Immune modulator (steroids) is among the wide range of drugs used in treating PID patients. Despite the difficulty in understanding how it works, it has a broad and rapid onset of effects on all major immune response actors (T, B, NK, neutrophils), as well as wound healing, glucose metabolism, and adrenal suppression. Cytokines therapy such as interferons for treating recurrent herpes simplex virus by Interferon Alpha (IFNα) and chronic granulomatous disease by Interferon Gamma (IFNγ) has been employed with varying degrees of success. Interleukin 2 is introduced as a therapeutic choice in immunodeficiency, particularly Wisskot Aldrich syndrome (WAS) **[65]**.

Rituximab (anti-CD20) is used to treat lymphoma and a variety of autoimmune illnesses. It works by depleting B cells and disrupting autoantibody synthesis, which might assist in treating CVID and CVID-related autoimmune cytopenias [66, 67].

Patients with ALPS benefit from mycophenolate mofetil, a prodrug of mycophenolic acid that inhibits inosine monophosphate dehydrogenase and suppresses T and B cells. ALPS is also antagonistic to sirolimus, a mechanistic target of rapamycin (mTOR) inhibitor that targets double-negative T cells [66, 68].

1.1.7 (d) Treatment by transplantation and gene therapy

i-Hematopoietic stem cell transplantation (HSCT)

Hematopoietic stem cell transplantation is a promising technique that relies on replacing PID patients' dysfunctional or depleted bone marrow cells with healthy donor hematopoietic stem cells (HSC). The process is preceded by a conditioning regimen that includes both serotherapy and chemotherapy in order to reduce the risk of graft rejection and graft versus host disease (GVHD). HSCT is a curative therapy option for patients with severe combined immunodeficiency (SCID). Wiskott-Aldrich Syndrome (WAS) and severe combined immunodeficiency (SCID) were the first PIDs to receive effective HSCT in 1968 [69, 70].

HSCT used to be a difficult procedure with high rates of morbidity and mortality. Nevertheless, the outcome of HSCT for PID has dramatically improved over time due to the advent of high-resolution HLA typing, expanded use of alternative donors, and new stem cell sources. Better patient outcomes are also linked to reduced-intensity conditioning (RIC) regimens that are less toxic and graft modification techniques based on cellular engineering that are now employed in HSCT. By utilising rapid

genetic testing using next-generation sequencing (NGS) tools, infants with SCID can be identified early from newborn screening programs before they develop infectious diseases. HSCT has been used to treat a broader range of PID, including immune dysregulation disorders, while new HSCT techniques are being developed to improve survival and long-term QOL.

ii- Gene therapy

Gene therapy is a retroviral gene transfer into PID patients' stem cells progenitor cells (HSC/Ps). In contrast to the requirements in the HSCT method, gene therapy does not require a suitable donor, no GvHD, and the hazards of myelosuppressive and immunosuppressive preconditioning of the patient. Nonetheless, gene therapy is currently in clinical trials, and more long-term data on the technique's safety are required before it can be used as a standard treatment for PID patients.

1.1.8 Survival outcome for PID

1.1.8 (a) Hematopoietic stem cell transplantation improved survival outcome

According to a study conducted in the United Kingdom between 1987 and 2012 involving 43 patients that received 49 transplants, 31 patients survived by August 2015. The median age was 10 years (range, 2-25 years). The overall survival at 10 years post-HSCT was 71.9% and transplant-related mortality (TRM) was 23.3% [71]. This comprehensive study supports the efficacy of HSCT as a curative therapy for a variety of primary immunodeficiency illnesses, exhibiting exceptional survival rates after transplantation from related and unrelated donors [72]. A retrospective study of 20 individuals who received HSCT for primary immunodeficiency was performed at the UK northern supra-regional HSCT center between 1998 and 2007, with a median

age at transplantation of 75 months (range – 21 years). After HSCT, 18 (90%) individuals were alive for 4 to 117 months (median = 61) with normal neutrophil function. Two died from disseminated fungal infection, and two had substantial GVHD [73].

Five-year survival rate was high for recipients of graft from matched sibling donors compared to recipients of graft from alternative donors, with no immunoglobulin replacement and CD3+ T-cell and IgA recovery. The survival rate was 94%, regardless of donor type among young infants (3.5 months) and 90% in older infants without prior infection or 82% in infants older than 3.5 months old with an infection that had resolved [74].

1.1.8 (b) Early neonatal screening improved survival outcome

The importance of early neonal screening on survival outcome was reported following the data gathered from two designated SCID transplant centers in the UK between 1982 and 2010. Patients were classified into two cohorts: sibling cohort (those SCID patients were diagnosed antenatally or at birth) and the proband cohort (those with SCID diagnosis after previous positive family history). The outcomes of both cohorts were better overall survival for the sibling cohort at 90% and death (10%) with 17% (n = 10) having a total of 12 infections and no cases of pneumocystis were documented. Meanwhile, the proband's survival rate was 40% with a 60% mortality rate [75].

1.2 Health-related quality of life

1.2.1 Definition

Health-related quality of life (HRQOL) encompasses domains such as physical, mental, emotional, and social functioning. It focuses on the influence of health status

on QOL rather than direct measures of population health, life expectancy, and causes of death. Well-being is a concept connected to HRQOL that evaluates a person's positive aspects. Hundreds of QOL measures have been created, the majority of which are used to assess HRQOL. For population and comparative research, generic measurements that apply to people with varying health statuses are preferable. Measures that are particular to disease have a high sensitivity and are best used for evaluation [76].

1.2.2 Definition Methods of health-related quality of life measurement

1.2.2 (a) Child Health Questionnaire (CHQPF50)

The Child Health Questionnaire (CHQPF50) is used to measure physical, psychological, and social functioning. The instrument assesses the emotional influence of a child's health on his or her parents, and the child's well-being. Higher scores indicate better functioning and well-being when converted to a 0–100 scale.

1.2.2. (b) Short Form-36

The Short Form-36 is a tool used mainly to measure generic health status. The questionnaire comprises 36 items that assess an 8-scale profile of health concept functional state variables.

1.2.2 (c) Paediatric Quality of Life Inventory (PedsQL 4.0)

The Paediatric Quality of Life Inventory (PedsQL 4.0) is the most commonly used tool for QOL in pediatrics. The instrument contains 23 items that are designed to measure QOL, including both a child's self-report and a parent proxy report. The items are transformed to a 0–100 scale using a 5-point answer scale.

1.2.2(d) Lansky's Play Performance Scale (LPPS)

The Lanky's Play Performance Scale (LPSS) is children's observational scoring scale that is based on the degree of play and activity. The instrument is designed based on the child's regular activities, relevant across age groups, and readily assessed with parent ratings.

1.2.2(e) Life Quality Index (LQI)

The Life Quality Index (LQI) was developed to assess PID patients receiving IVIG therapy, and then utilised in SCIG treatment. The instrument comprises 15 items, with ratings on a 7-point Likert scale ranging from 1 (extremely terrible) to 7 (highly good).

1.2.3 Practical implications of health-related quality of life surveillance

Surveillance of HRQOL is important to monitor changes in peoples' health. a large study conducted in 50 states in USA and the district of Colombia revealed that all the participants rated their health as fair or poor [77]. The findings were based on the data collected from both the Behavioural Risk Factor Surveillance System (BRFSS) from 1993 to 2001, and the National Health and Nutrition Examination Survey (NHANSS) from 2001 to 2002. Furthermore, individuals who were unable to work, those with a household income of less than $15,000, and those with less than a high school degree all showed lower HRQOL (i.e., physically unhealthy days, mentally unhealthy days, overall unhealthy days, and activity limitation days). Younger participants reported more psychologically unwell days, wheras older adults reported more physically unhealthy days and activity limitation days [77].

1.3 Research Question(s)

(1) How is the QOL among patients and families with PID in Malaysia?

(2) What is the social issue among PID patients and families with low QOL?

1.4 Objectives

1.4.1 General

To determine the QOL and contributing factors of PID cases in Malaysia

1.4.2 Specific

(1) To compare the mean PedsQL score between PID children and normal children.

(2) To compare parental perception based on PID child's mean PedsQL score.

(3) To predict determinants for mean parental PedsQL score of PID child based on demographic, type of PID, and level of immunoglobin replacement therapy.

(4) To predict determinants for mean child PedsQL score of PID child based on demographic, type of PID, and level of immunoglobin replacement therapy.

(5) To explore social issues among selected PID patients and families with low QOL.

1.5 Study Hypothesis

Hypothesis H1= Patients and families with PID in Malaysia have low QOL.

Hypothesis H0= Patients and families with PID in Malaysia have normal QOL.

CHAPTER TWO

LITERATURE REVIEW

2.1 Health-related quality of life in PID

2.1.1 Worldwide vs Malaysia

HRQOL is becoming increasingly recognised as a factor that affects patient well-being and treatment preferences compared to other chronic disease patients who have restrictions in their physical, emotional, and social functioning. The World Health Organisation defines QOL as an individual's sense of their place in life concerning their objectives, expectations, standards, and worries, as well as the culture and value systems in which they live [78]. The field of oncology was the first to use HRQOL assessments [79].

From 1979 to 2020, Malaysia's estimated prevalence of PID was 0.37 per 100,000 people [5]. The commonest causes of PID in Malaysia are specific antibody defects as per a report published in 2013 [6]. However, no survey or data on health-related quality of life among PID patients in Malaysia has been published to date. HRQOL has been studied extensively in Europe and the USA. Abd Hamid et al (2013) demonstrated that QOL in PID post-hematopoietic stem cell transplant survivor was better in those without long-term comorbidities [12, 80]. Patients with PID have much inferior general health than healthy children and adults, with greater hospitalisation rates and physical, school, and social activity limits [81].

From previously published reports, child-rated and parent-rated assessments revealed that children with PIDs had significantly lower HRQOL total scores compared to children with Juvenile Idiopathic Arthritis and healthy children [82]. As

reported by parents, PID children also demonstrate a considerably higher incidence of depression and anxiety symptoms [83].

Table 2.1: Positive and negative impact factors on HRQOL in patients with PID [84].

Factors negatively impacting the quality of life in PID patients	Factors positively impacting the quality of life in PID Patients
Delay in diagnosis	Treatment in the home setting
Other chronic health issues / Chronic lung disease	Independence
Stress	Convenience of treatment
Unemployment	Comfort of treatment
Repeat infectious episodes	Less parental impact time
Social factors such as unemployment	Therapeutic IgG trough levels

2.1.2 HRQOL according to specific PID diagnosis

2.1.2. (a) Predominantly Antibody Defects

Findings regarding predominantly antibody defects can be gleaned from a study conducted in the UK for children with predominantly antibody deficiency (PAD) using Modified chronic fatigue syndrome (CFS) questionnaires [85]. The data were collected from the UK PID registry with CVID (162 patients, 86%) X-linked agammaglobulinemia (12 patients, 6%). Over one-third of the patients exhibited radiographic evidence of lung damage, with 60% and 40% of the 188 patients receiving SCIG and IVIg, respectively. The number of patients receiving home immunoglobulin therapy was comparable to those receiving treatment in hospitals. A high number of PAD patients experienced symptoms that were consistent with a diagnosis of CFS.

In the study, no difference was recorded in the prevalence of CFS symptoms among participants on SCIG against those on IVIg, and among patients on home

therapy versus those undergoing treatment in the hospital. About 16.3% of patients scored 8 out of 13, with more than 31.9% of patients scoring borderline marks (6–7/13). The mean CFS score of patients with severe exercise intolerance was substantially greater than that of individuals with mild exercise intolerance [85].

2.1.2. (b) Severe Combined Immunodeficiency

In the HRQOL study performed in the UK involving children with severe combined immunodeficiency (SCID) who had undergone hematopoietic stem cell transplantation, no significant discrepancies were reported between the self-reporting of patients and UK published norms. However, 17 parents reported significantly worse QOL in the overall, psychosocial, and school categories. Meanwhile, no significant difference in QOL between children who received weekly subcutaneous immunoglobulin infusions at home and those who did not [71].

2.1.2. (c) Chronic Granulomatous Disease

The Italian registry for Chronic Granulomatous Disease (CGD) enrolled 19 children and 28 adults, with the children and caregivers using PedsQL and the stress and difficulty questionnaire (SDQ), whereas adults used the short-form (SF-12) questionnaire [86]. Parents of younger children (five years of age) reported more challenges in social/school areas, peer interactions, and conduct/emotional problems. CGD adults reported more difficulties in both mental and physical areas than the general population. The clinical state showed a negative impact on children's psychosocial and school characteristics. There was no discernible difference between patients who had HSCT and those who did not. Physical disabilities were less common among CGD children and adults. In comparison to patients with diabetes mellitus and