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PRIMARY IMMUNODEFICIENCY DISEASE IN MALAYSIA: WHERE ARE WE NOW?
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Abstract
Primary Immunodeficiency Diseases (PIDs), also called Inborn Errors of Immunity (IEI), are a group of diseases caused by a single gene defect affecting the differentiation or development of the immune system. These diseases usually manifest with increased susceptibility to infections, autoimmunity, autoinflammatory diseases, allergy, bone marrow failure, and/or malignancy. The PID Life Index is a unified continuum of PID care aimed at reducing inter-country gaps and improving patients’ care outcomes. In Malaysia, there has been significant progress in PID care in close to half a century since the first case of PID was discovered. On the other hand, there are bottlenecks facing the progress in PID care in Malaysia. This review was written to assess PID care in Malaysia based on the six components of the PID Life Index.

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Introduction
Primary Immunodeficiency Diseases (PIDs), also called Inborn Errors of Immunity (IEI), are a group of diseases caused by a single gene defect affecting the differentiation or development of the immune system. The defects result in over 480 diseases, each with its manifestations which include increased susceptibility to infections, autoimmunity, autoinflammatory diseases, allergy, bone marrow failure, and/or malignancy [1]. The spectrum of PID has rapidly expanded over the years.

The incidence of PID has proportionately increased with the increase in awareness of PID among physicians and increased diagnostic tests. Thus, the incidence is higher in countries with high physicians’ awareness of PID and the availability of diagnostic tests such as Next Generation Sequencing (NGS). The overall prevalence of PID is 1:10,000 [6,7]. The prevalence varies, from 1:1,200 persons was reported in the United States population [8], to less than 1:100,000 in African countries (due to underdiagnosis) [9].

The care of PID patients widely varies across countries and continents. As an action for a unified method of PID care aimed at reducing the inter-country gaps and improving PID care, six-package principles of care (PoC) were developed in 2014 [10]. The components of the PoC are: 1) the role of specialized centres; 2) the

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importance of registries; 3) the need for multinational research; 4) the role of patient organizations; 5) the need for sustained access to all treatments, including immunoglobulin (Ig) therapies and HSCT; and 6) managing PID in all countries [10]. In 2020, the International Patient Organisation for Primary Immunodeficiencies (IPOPI) revised the PoC into indices for assessing global PID PoC, called the PID Life Index. The six components of the PID Life Index are: 1) availability of diagnosis; 2) availability of treatment; 3) universal health coverage; 4) national specialised centres; 5) national patient organisations and 6) national registries [11,12]. Despite the recent developments and advances in PID, there are challenges facing PID diagnosis and care in Southeast Asian countries [13]. We hereby review PID care in Malaysia based on the Life Index PoC.

PID in Malaysia
Malaysia is a country in Southeast Asia. According to the WHO (2020), Malaysia has a population of 33 million, a life expectancy of 74.7 years, an infant mortality rate of 6.46 per 1000 live births, and an under-5 mortality rate of 7.56 per 1000 live births [14]. The first case of PID was reported by Yadav et al. in 1977 when they reported a decrease in the immunoglobulin A (IgA) level of a 10-year-old girl with bronchiectasis [15]. There has been significant progress in the past four and a half decades since the first case of PID was reported in Malaysia. As of 2020, a prevalence of 0.37 per 100,000 people was reported from a systematic review of 34 publications [16]. The low prevalence of PID in the review may be the tip of the iceberg due to possible underdiagnosis and a lack of a national PID registry, as a higher prevalence of PID was reported in Asian countries with PID registries [17]. Based on the estimate of 1 PID case per 2,000 population [11], the population-based theoretical prevalence of PID in Malaysia is 16,183. Out of these, only 200 cases are currently diagnosed [18]. This underscores the gap in PID case diagnosis and reporting in Malaysia.

Among the groups of PIDs, a systematic review of Malaysian studies was performed and found that cellular and humoral immunodeficiencies are the most prevalent (30.3%) followed by predominantly antibody deficiencies (20.2%) [16]. Noh et al. had earlier reported higher antibody deficiencies (40.4%) followed by phagocytic defects (17.3%) [19].

Progress and challenges in PID care in Malaysia, The Life Index Themes:

PID diagnosis in Malaysia
The diagnosis of PID plays a pivotal role in the management of PID patients. The PID diagnostic methods are broadly categorised into four: biological tests, genetic diagnosis, prenatal tests and newborn screening [11]. The accessibility and affordability of these diagnostic tests, the awareness of the disease among physicians, especially at the primary healthcare level, and the awareness of diagnostic tests among patients and/or their parents are important factors in PID diagnosis [20].

There has been significant progress in the diagnosis of PID in Malaysia. Previous diagnoses were reported without confirmatory genetic tests [21,22]. Lately, Next Generation Sequencing (NGS)such as whole exome sequencing and targeted panel sequencing have been conducted on PID patients [23,24]. Biologic tests are available in the few centres that offer PID care [25]. Genetic testing is being conducted in some centres in Kuala Lumpur, while prenatal and newborn screening are not being implemented yet.

Although there has been progress in genetic diagnosis of PID in Malaysia, it is still sub-optimum. Abd Hamid et al. reported that only 21.8% of patients had genetic tests in Malaysia [16]. Few centres have the capacity for the test on an out-of-pocket payment basis. This was corroborated by data from IPOPI (genetic tests available in 25% of cases) [18], and Leung et al. (reported low genetic testing in Malaysia, which is lower than most Asian countries with a very high human development index) [26]. Even when the diagnostic tests are available, there is a delay in diagnosis. For instance, Ripen et al. found a median of 4 years from the onset of symptoms to diagnosis [24], while Noh et al. reported an average of 3.87 years [19]. This delay is more worrisome in diseases like Severe Combine Immune Deficiency (SCID), where early diagnosis and treatment improve outcomes. In SCID, neonatal screening is the mainstay because a delay in therapy commonly leads to death before the first birthday, usually from infections. Unfortunately, there is no routine neonatal screening for SCID in Malaysia [18,25].

Availability of PID treatment in Malaysia
Treatment of PID varies with the individual disease. Treatment can be supportive or curative. The main supportive PID treatments are Immunoglobulin Replacement Therapy (IRT) and anti-infectious therapy while definitive therapies are Hematopoietic Stem Cell Transplantation (HSCT), gene therapy and thymic transplant. Other ancillary therapies include biological factors: like growth factors, interleukins/cytokines, thrombopoietin receptor agonists, C1 inhibitor concentrate, monoclonal antibodies, immunosuppressors and immunomodulators, and enzyme replacement therapy for adenosine deaminase deficient SCID [11].

Anti-infectious therapy involves the use of antimicrobial drugs, usually prophylactically, but sometimes therapeutically. As in most countries, anti-infectious therapy is available and accessible in Malaysia, though affordability is not universal.
Immunoglobulin therapy is commonly used in patients with antibody deficiencies, which is one of the most common PIDs in Malaysia. Laudably, Intravenous Immunoglobulin (IVIg) is freely available in the specialised PID centres in Malaysia [17,25]. But the centres are few and unevenly distributed. Subcutaneous immunoglobulin (SC Ig) is administered subcutaneously by patients and caregivers at home after training. Thus, it may be a better option for some patients because, unlike IVIg, SC Ig does not require hospital admission. As with most countries, SC Ig is not widely available in Malaysia [25]. Targeted pathway blocker therapy for activated PI3K delta syndrome has been started in Malaysia recently (unpublished data).

Hematopoietic Stem Cell Transplantation (HSCT) is a lifesaving and definitive therapy for PIDs like SCID and Wiskott-Aldrich syndrome. In Malaysia, HSCT commenced 2 decades ago, yet only a few hospitals have the capacity to conduct it. There is also a dearth of data on the number of HSC Ts conducted in the country, likely due to lack of National PID patients Registry. Ariffin et al. reported 20 cases of HSCT for PID in Malaysia with positive outcomes [27].

**Specialised Centres for PID Care in Malaysia**

According to the PID Life Index, a specialised centre should “… reach internationally agreed standards of care and offer a holistic approach to the diagnosis, treatment, and care of patients with PIDs [11]. There should also be good networking and referral systems between specialised centres and transition systems from paediatric to adult care [10,11]. Some centres fulfil these criteria in Malaysia. Over the years, these centres have changed the narratives on PID to a positive outlook. However, with increasing cases of PIDs, Malaysia is facing a scarcity of clinical immunologists to manage the cases diagnosed. As of 2019, Abd Hamid et al. reported that there are only five clinical immunologists in Malaysia, giving a ratio of 1 clinical immunologist to 6.48 Malaysian population. Moreover, all the clinical immunologists except one, were practising in Kuala Lumpur [25]. Five years later, the story has not changed. In an interview published on a health site, Abdul Latiff (2024), stated that Malaysia has only seven clinical immunologists, six of whom are within the Klang Valley, one in Penang [28]. It is also alarming that currently, there is no single adult clinical immunologist in a government hospital to enable a smooth transition of patients from paediatric to adult care, raising concerns from both clinicians and patients [29]. In the same vein, Noh stated that a 17 year struggle for the establishment of a clinical immunology subspecialty in Malaysia as a means to achieve the desired number of immunologists to care for the increasing number of patients beyond PID is yet to yield fruit [28].

**National Patient Organisations**

In general terms, patients and carers play a central role in their care, as the management of diseases is becoming more patient-centred. This is more pronounced in PID, which is a chronic disease requiring both preventive and supportive treatment measures. Patient organisations are key stakeholders in PID care. For instance, the IPOPI played a leading role in the development of the PID Life Index. The Malaysian Patient Organisation for Primary Immunodeficiencies (MyPOPI!) will be 20 years old in August this year. The organisation has over 100 members and has been actively participating in improving PID care in Malaysia. MyPOPI! contributes significantly to the IPOPI’s Life Index, having the highest score amongst all the six PID indices in Malaysia [18].

**National PID Registry**

A PID national registry will help in the collection and interpretation of national epidemiologic data on PID, such as prevalence and incidence data, through networking with PID specialists, specialised centres and other diagnostic centres [10]. Such data will help in policymaking, research and the development of treatment. A registry for PID previously reported 200 cases of the disease. Currently, there is no national PID registry in Malaysia. This has affected research and policy-making. For instance, the exact number of diagnosed PIDs is unknown. The prevalence of PID reported by Abd Hamid et al. was from a systematic review of 34 Malaysian studies. In the review, the authors acknowledged the limitation of the prevalence of PID calculated because some of the diagnosed cases may not have been published, thus giving a low prevalence. The reviewers, therefore, concluded with a call for a national PID registry in Malaysia [16].

**Universal health coverage**

Universal Health Coverage (UHC) are defined as “all people have access to the full range of quality health services they need, when and where they need them, without financial hardship. It covers the full continuum of essential health services, from health promotion to prevention, treatment, rehabilitation, and palliative care across the life course” [30]. The achievement in terms of UHC varies significantly across countries. Because UHC is not targeting PID alone, developing countries facing other health challenges such as endemic infectious diseases like tuberculosis, malaria and HIV are facing challenges in PID UHC care [11].

Universal health coverage for PID should reimburse the costs of all diagnoses and treatments. Based on the PID Life Index, the UHC coverage in Malaysian PID patients is at 26%. Malaysia has a reimbursement cost of 91-100% for growth factors and 51-69% for HSCT [13]. It also has free IVIg therapy for PID patients.
receiving healthcare in the government based healthcare facilities. However, reimbursements for other diagnostic tests and treatments are low.[13]

Conclusion
There has been positive progress in PID care in Malaysia based on the PID life index. However, despite the achieved progress in PID care, some gaps need to be filled. A concerted involvement and effort from various stakeholders are urgently needed for an improved quality of care for PID patients.

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