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PRIMARY IMMUNE DEFICIENCY DISEASE IN SAUDI CHILDREN: SYSTEMATIC REVIEW

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ABSTRACT

The study aims to summarize current evidence regarding the primary immune deficiency disease in Saudi children. The PubMed database Information Services was utilized for article selection. In our review, we used all relevant articles related to our issue as well as unrelated publications. Other papers that were unrelated to this field were not considered. The data was extracted in a specified format, which the group members examined. Literature shows from the table it is clear that Combined immunodeficiencies were the most common (59.7%), followed by Phagocytic disorders (57.2%) then, predominantly antibody deficiencies (12.3%) among our PID patients. There was no difference in the frequency of B-cell and T-cell abnormalities. PID is not infrequent in Kuwait. Kuwaitis had a prevalence of 20.27/100,000, with a cumulative incidence of 24.96/100,000 Kuwaitis. The estimated frequency in Tunis was 4.3 per 100,000 people. Collaborative measures, such as the implementation of newborn screening, should be conducted to detect such instances early, enhance the quality of life, and avoid untimely deaths. The most prevalent were combined immunodeficiencies (59.7%), followed by phagocytic diseases (57.2%) then, predominantly antibody deficiencies (12.3%) among our PID patients. Collaborative measures, such as the implementation of newborn screening, should be conducted to detect such instances early, enhance the quality of life, and avoid untimely deaths. More systematic, multicenter, large-sample prospective studies with a larger sample size are necessary.

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Introduction

Primary immunodeficiency disorders (PID) are a category of over 300 unique illnesses caused by various genetic defects that impact immune system development and/or function [1]. The precise frequency of PID is unknown due to a lack of screening, national registries, or reporting by government health surveys in many countries; nonetheless, a PID prevalence of about 1:10.000 has been observed in Australian, North American, and European populations [2].

Primary immunodeficiency diseases (PID) are uncommon genetic abnormalities that predispose individuals to repeated infections, autoimmunity, and cancers. As a result, creating a database is critical for determining the size, kinds, and range of PID illnesses in a given community. Similar databases throughout the world have revealed geographical and ethnic variations in the range of PIDs [3]. Saudi registry data are limited to two research. Both are from a homogenous population and only one section of the country, and hence do not likely reflect the entire nation [4].

Nonetheless, these are significant early findings that underscore the importance of continued, systematic data collecting in order to be more familiar with PIDs in Saudi Arabia. Additionally, consanguineous marriages (first-cousin weddings) are common in Saudi Arabia, accounting for up to 60% of all marriages. This has created the conditions for hereditary illnesses to be prevalent in the Saudi population. Studies of a reasonably significant amount of individuals found with an autosomal recessive hereditary type of PIDs, such as severe combined immunodeficiency (SCID), hyper-IgE syndrome, and hyper-IgM

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syndrome, revealed an increased prevalence of consanguineous marriages. It was shown that for febrile children and those having SCD, the most preferred broad spectrum antibiotic is ceftriaxone. In dermatology, JAK inhibition has been investigated in a range of conditions known to have auto-immune involvement such as psoriasis and atopic dermatitis (AD).
As a result, registry data from Saudi Arabia is critical, particularly for autosomal recessive inherited PIDs [5]. Furthermore, the general prevalence of combined immunodeficiencies (CID) is projected to be 1 in 75,000 to 100,000 live births; however, because higher percentages of CID are inherited as autosomal recessive traits, anecdotal evidence recommends that the prevalence of CID is more in the parts we live as compared to western Nations, likely exceeding 1 in 10,000 live births. Though, precise epidemiologic data are still sparse [6].

Study Objective
The study's objective was to explore and summarize the current and updated evidence on primary immune deficiency disease in children in Saudi Arabia.

Materials and Methods

Study Design
It was systematic review.
Systematic review is a technique for compiling previously published studies to synthesize suggestions on a subject; it is frequently utilized in the health disciplines to identify novelties and then discover new approaches to health services, enabling the utilization of evidence-based health care, guaranteeing high-quality services, and enhancing patient welfare and safety. Six sequential stages require to be followed: Explanation of the study issue; inclusion and exclusion criteria; sample definition; evaluation of included studies; findings interpretation; and presentation of the ILR synthesis.
After locating and defining the sample, the publications with the same purpose as our study were thoroughly examined.
Due to their reputation as reliable databases, PubMed and EBSCO Information Services were chosen as research databases for the publications used in the study. One of the biggest online digital libraries, The National Center for Biotechnology Information (NCBI), a part of the National Library of Medicine in the United States, founded PubMed. The article was created using subjects relating to primary immune deficiency disease in Saudi children. The topics and summaries of the established papers were scrutinized.
The subjects were selected for addition, decided for their applicability to the research, which must have at least one of the following subjects; immune deficiency, primary immune deficiency disease, PID, and Saudi children.

Exclusion Criteria
All further publications, recurrent studies, and research reviews that did not have one of these topics as their primary goal was excluded.

Analysis of Data
No software was utilized to analyze the data. The data was extracted from a predefined format that includes the study subject, author's designation, goal, executive summary, results, conclusions, and outcomes. To guarantee rationality in addition to reducing errors, the results of each affiliate was double-revised.
The included studies were double-reviewed during the article selection process to verify that the research contained inside the study is related to the target line of our study and to avoid or minimize slips in the results.

Results and Discussion

Figure 1 shows the selection and identification of studies. A total of 314 studies were included for title screening after a search of the aforementioned databases. 211 were chosen for abstract screening, resulting in the removal of 132 articles. The remaining 79 full-text articles were examined. Because of differences in research aims, 72 papers were excluded during the full-text editing, and only seven were enrolled for final data extraction **(Table 1)**.
According to the table, combined immunodeficiencies were the most prevalent (59.7%), followed by phagocytic diseases (57.2%), and then primarily antibody deficiencies (12.3%) among our PID patients. No difference existed in the frequency of B-cell and T-cell abnormalities. PID is not uncommon in Kuwait. Kuwaitis had a prevalence of 20.27/100,000, with a cumulative incidence of 24.96/100,000 Kuwaitis. The estimated frequency in Tunis was 4.3 per 100,000 people.

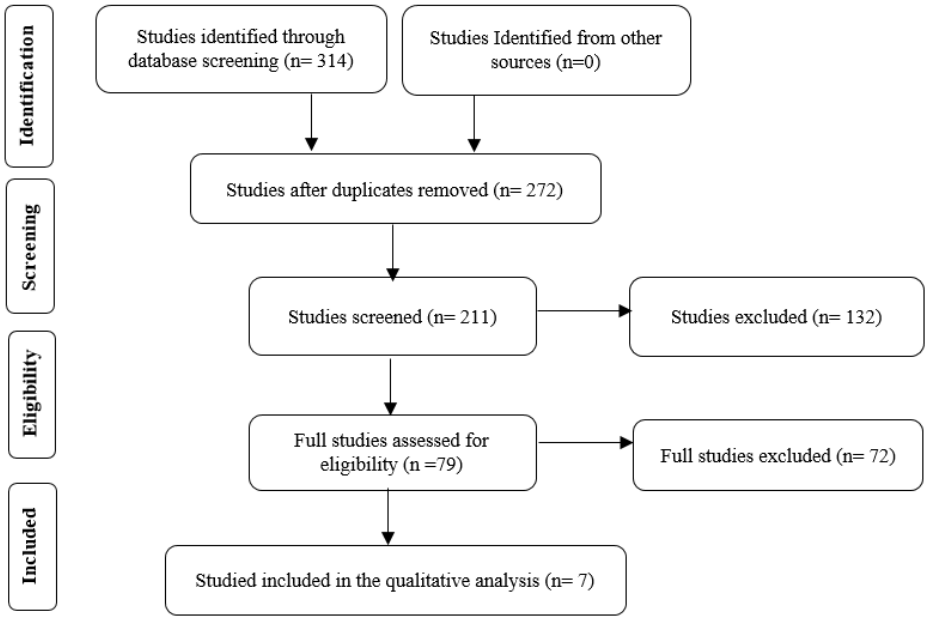

Figure 1. The included studies had different study designs

Table 1. Author, country, year of publication, methodology, and outcome

Author, publishing year	Study region	methodology	outcome
Khalilzadeh *et al*, 2011 [7]	Masih Daneshvari hospital	A review of patients' medical data was used in this retrospective investigation. Clinical, laboratory, and epidemiological data, as well as personal and family histories were collected by analyzing patients records admitted to the NRITLD Pediatric Pulmonary Unit, a TB and lung disease referral centre. The WHO criteria for primary immunodeficiency diseases were used to make the diagnosis.	The information gathered from 59 patients was assessed and analysed. There were 35 men (59.3%) and 24 women (40.69%). The patients' ages varied from 6 months to 14.5 years, with 7.4 years mean. A positive family history was found in 20 cases (33.9%), and 36 (61.2%) had consanguineous patients. Twenty (33.9%) of the patients had a family history of PID. The most prevalent kind of PID was phagocytic disease (57.2%), followed by antibody deficit (33.7%) and T-cell or mixed deficiency (8.2%). There was no evidence of complement insufficiency. Two individuals in this group died of respiratory failure due to drug-resistant pneumonia (chronic granulomatosis).
Al-Saud *et al*, 2015 [8]	Saudi Arabia	From May 2010 to April 2013, all PID patients monitored at the King Faisal Specialist Hospital & Research Center (KFSH&RC) were interviewed and their medical records were reviewed.	The most common was combined immunodeficiency (59.7%), followed by antibody deficiency (12.3%), congenital phagocytic disorder (9.4%), combined immunodeficiency with associated or syndromic features (6.2%), impaired immune dysregulation (6%), complement system deficiency (5.8), and defects in innate immunity (0.6%). T-B-SCID (17%) was the most prevalent phenotype of combined immunodeficiency. Patients' ages ranged from <1 year to 78 years, with 394 (78.2%) falling into the pediatrics age group (14 years). The median age of onset was 17 months, while the median delay in diagnosis was 21.6 months. The most prevalent clinical manifestation (66%), followed by family history (26%), was recurrent infections. 75% of patients were consanguineous. A total of 308 patients (61%) underwent stem cell transplantation (SCT).
Rubin *et al*, 2018 [9]	United States	From 2003-2012, a retrospective cohort analysis of children aged 2-18 years hospitalized with a primary or secondary diagnostic code PIDD was performed. Secondary immune deficiency diseases were not considered.	From 2003 to 2012, there were 26,794 paediatric children hospitalised with a PID diagnosis. Children aged 0 to 5 years had the highest prevalence (15,105 hospitalizations; 56%). There was no difference in the frequency of B-cell and T-cell abnormalities. PIDDs had an equivalent impact on all ethnic groups. The most prevalent comorbidity by organ system was respiratory-related diagnoses. The overall mortality rate was 1.99%. Age was shown to be inversely associated to clinical outcomes. Children aged 0 to 5 years had a higher death rate.

Al-Herz *et al*, 2019 [10]	Kuwait	Between January 2004 and December 2018, the patients were tracked prospectively, and the data gathered comprised sociodemographic, diagnostic, clinical presentation, laboratory testing, and therapy information.	During the research period, 314 PID patients (165 males and 149 females) were recorded. The majority of the patients (n = 287, or 91.4%) were Kuwaiti citizens, with a frequency of 20.27/100,000 Kuwaitis and a cumulative incidence of 24.96/100,000 Kuwaitis. The patients were distributed as follows according to PID categories: 100 patients (31.8%) had immunodeficiencies affecting cellular and humoral immunity; 68 patients (21.7%) had combined features of immunodeficiency and related syndromes; 56 patients (17.8%) were antibody deficient; 47 patients (15%) had immune dysregulatory disorders; 20 patients (6.4%) had autoinflammatory disorders, and 22 patients (7% had complement deficiencies). Patients had a median age at onset of 26 months, a median age at diagnosis of 53 months, and their mean delay in diagnosis was 27 months. Symptoms appeared in most patients (n = 272, 86%) before the age of five. Parental consanguinity was found in 78% of the recorded cases, and 50% had a positive family history of PID. Genetic testing was completed on 69% of the patients, yielding a 90% overall diagnosis yield. Mutations were found in 46 distinct genes, with autosomal recessive inheritance accounting for more than 90% of the observed genetic abnormalities. In 58% and 25% of the patients, intravenous immunoglobulins and stem cell transplantation were employed, respectively. Among the recorded patients, there were 81 fatalities (26%) with a mean age of death of 25 months.
Mellouli *et al*, 2015 [11]	Tunis	Over a 25-year period, we evaluated the records of 710 individuals diagnosed with Primary Immunodeficiency Diseases (PIDs) from the Tunisian Referral Centre for PIDs registry.	The male-to-female ratio was 1.4. The median age at onset was 6 months, and the median age at diagnosis was 2 years. The predicted prevalence was 4.3 per 100,000 population. Consanguinity was discovered in 58.2% of families. The International Union of Immunological Societies (IUIS) has classified PID as: combined T-cell and B-cell immunodeficiency disorders (28.6%), congenital defects of phagocyte (25.4%), other well-defined immunodeficiency syndromes (22.7%), predominant antibody deficiency disorders (17.7%), immune dysregulation diseases (4.8%), innate immune disorders (0.4%), and complement deficiency (0.4%). The most prevalent symptom of PID patients was recurrent infections, particularly lower airway infections (62.3%). The total death rate was 34.5%, with coupled immunodeficiencies being the most common cause.
Wu *et al*, 2019 [12]	China	From January 2013 to November 2018, 112 children with PID were identified and categorised in a single tertiary care hospital using the 2017 International Union of Immunological Societies (IUIC) standards. We evaluated the clinical characteristics of those PID children retrospectively and followed them up.	The male/female ratio was discovered to be 6:1. The most common PIDs were severe combined immunodeficiency (28.6%) and hyper-IgM (HIGM) syndrome (24.1%), followed by antibody deficiencies (17.8%). When compared to SCID and HIGM syndrome, combined immunodeficiencies with related or syndromic characteristics (12.5%) and congenital abnormalities of phagocyte quantity, function, or both (10.7%) were less prevalent in our centre. Furthermore, we discovered that 20 children (17.8%) had a positive family history of PID, and nearly all cases (97.3%) had a history of recurrent infection. Recurrent respiratory infections were one of the most prevalent signs, followed by bacterial skin and mucosal infection and diarrhea. Furthermore, 20.5% of the patients had an adverse event following vaccination (AEFI), and immunological disorders were frequent in PID patients. In the current study, 47 patients had allogeneic hematopoietic stem cell transplantation (allo-HSCT), with a 2-year overall survival (OS) rate of 78.7% (37/47). It is worth noting that OS varied greatly among PID patients with diverse characteristics who had allo-HSCT. SCID, HIGM syndrome, and the remaining PID patients who had allo-HSCT had 2-year OS rates of 14.3, 83.3, and 100%, respectively.
Aghamohammadi *et al*, 2014 [13]	Iran	This study offers demographic information and clinical signs of Iranian PID patients diagnosed between March 2006 and March 2013 and reported in the Iranian PID Registry (IPIDR) following its second report in 2006.	The current study included 731 new PID patients (455 male and 276 female) from 14 different medical facilities. The most common subcategory of PID was antibody deficiencies (32.3%), followed by combined immunodeficiencies (22.3%), congenital defects of phagocyte number, function, or both (17.4%), well-defined immunodeficiency syndromes (17.2%), autoinflammatory disorders (5.2%), diseases of immune dysregulation (2.6%), defects in innate immunity (1.6%), and complement deficiencies (1.4%). The most frequent condition was severe combined immunodeficiency (21.1%). Other frequent conditions were common variable immunodeficiency (14.9%), hyper IgE syndrome (7.7%), and selective IgA deficiency (7.5%).

Al-Tamemi *et al*, 2016 [14]	Oman	Sultan Qaboos University Hospital (SQUH) is an academic tertiary care hospital that treats patients with PID. Patients' sociodemographics, clinical aspects, laboratory tests, and treatment were all entered into a computerized database at the time of diagnosis. Patients visited between August 2005 and July 2015 were included in this research.	A total of 140 cases were registered, with an estimated population frequency of 7.0/100,000. The male/female ratio was 1.6:1, the median age of beginning of symptoms was 8 months, and diagnosis occurred after 21 months with a 13-month delay. Family history was present in 44%, consanguinity was present in 76%, death of a preceding sibling was present in 36%, and overall mortality was present in 18%, with an 85% chance of surviving 10 years after diagnosis. Phagocytic disorders were the most common type of immunodeficiency (35.0%), followed by antibody disorders (20.7%), combined immunodeficiency (17.8%), other well-defined PID syndromes (15.0%), immune dysregulation syndromes (3.5%), complement deficiencies (3.5%), and unclassified immunodeficiency (4.2%). Pneumonia was the most prevalent presenting illness (47.1%).

A study conducted in Iran revealed that there are different etiologies and risk factors that affect the frequency of PID. During 20 years, Farhoudi and colleagues detected 247 instances of PID among children (53.3% - 130 cases) and adults in comparable research at one of Tehran's university hospitals. However, there is no precise data on the prevalence of PID in Iranian youngsters [15].

A similar study was done in Israel in 2002, the study monitored 11 hospitals for 7 years, and they reported 249 cases of PID [16].

A study conducted in 2002 by Golan *et al*. revealed a Male / Female ratio of 2/1. Another literature found a 4/1 ratio. The increased prevalence in males can be further described by x-linked illnesses like CGD, Wiskott-Aldrich syndrome, hyper-IgM, as well as SCID.

The most common complaint in PID patients is infection. Infections of all kinds can develop; however, recurring and chronic respiratory infections are the most prevalent symptoms. Other infections present include diarrhea, abscess, septic arthritis, sepsis, and meningitis. The most common types of infection, according to the Iranian study, were respiratory, cutaneous, and gastrointestinal (GI) [17]. Positive family history was also discovered in 33.9% of PIDs who have phagocytic abnormalities.

A research conducted in Taiwan in 2005, the most common abnormalities observed were antibody deficiency (46%), T-cell or combination deficit (30%), and phagocytic abnormalities (24%), with no instances of complement deficiency [18].

A comparable investigation was conducted on 930 patients listed in the Iranian PID registry in 2006. The most prevalent deficiencies, according to this study, were antibody deficit (38.4%), phagocytic system defect (28.3%), T-cell or combination deficiency (11%), complement system abnormalities (2.4%), other immune system diseases (17.7%), and immunological dysregulation illness (2.3%) [19].

The general incidence of the insufficiency seen in the complement system is quite low; in different nations, the percentage is close to 2-7% [20].

CVID (75%) was the most common abnormality among the antibody deficiency syndromes, a finding that was consistent with research undertaken in Spain, Sweden, and Iran [21].

According to some accounts, IgA deficiency is the most prevalent characteristic of PID; European studies show a frequency of 33-50%.

SCID cases were less in number as compared to previous studies, which might be owing to the increased death rate of mentioned individuals at such a tender age [22].

Early detection and treatment of PID are very crucial in reducing infections, morbidities, and hospitalization in PID patients. The need for enhancing the understanding of detecting primary immunodeficiency diseases is vital for both diagnosis and also improved patient care and for minimizing potential sequelae [23].

Conclusion

The most prevalent were combined immunodeficiencies (59.7%), followed by Phagocytic disorders (57.2%) then, predominantly antibody deficiencies (12.3 %) among our PID patients. Collaborative measures, such as the implementation of newborn screening, should be conducted to detect such instances early, enhance the quality of life, and avoid untimely deaths, more systematic, multicenter, large-sample prospective studies are required.

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