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Clinical and Laboratory Profile in Different Types of Primary Immune Deficiency Disorders (PIDs) in Children: A BMU Perspective

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Abstract

Background

Primary immunodeficiency disorders (PIDs) constitute a heterogeneous group of immune defects with diverse clinical presentations. Timely diagnosis relies on integrated clinical and laboratory evaluation. This study aimed to describe the clinical and laboratory profiles of patients with suspected PIDs.

Results

A definitive diagnosis of PID was confirmed in 69 of 143 patients (48.2%). The mean age at diagnosis was 63.65 ± 57.01 months, with a diagnostic delay of 46.83 ± 31.27 months and a male-to-female ratio of 1.4:1. Common presentations included failure to thrive and frequent use of intravenous antibiotics. Antibody deficiencies were the most prevalent type (43.5%), followed by combined immunodeficiencies with syndromic features. Total leukocyte count was markedly elevated in chronic granulomatous disease. Absolute lymphocyte count was low in severe combined immunodeficiency, combined immunodeficiency, and severe congenital neutropenia. Immunoglobulin levels were significantly lower in combined and humoral immunodeficiencies compared to other PID types and non-PID patients. Recurrent pneumonia, persistent oral thrush, and the need for intravenous antibiotics were significant risk factors for PID.

Conclusions

In this cohort, antibody deficiency disorders and combined immunodeficiencies with syndromic features were the most common forms of PID among suspected cases. The significant diagnostic delay highlights the need for increased physician awareness and prompt referral for early diagnosis, which may help reduce morbidity and mortality.

Background

Primary immunodeficiency disorder (PIDs) or Inborn errors of immunity (IEI) is a large heterogenous group of genetic disorders characterized by dys-regulation of one or more elements of the immune system, that predispose individuals to a wide spectrum of infection and non-infectious complications like autoimmunity, allergy, auto-inflammation, lymphoproliferation, malignancy, clinically recognizable syndromes, and end-organ damage causing chronic dysfunction[1].

The spectrum of PIDs is evolving rapidly, with new PIDs continually being described and molecularly characterized. The updated classification compiled by the International Union of Immunological Societies (IUIS) Expert Committee in 2024 documents the key clinical and laboratory features involving 508 different genes and 17 phenocopies. In this update, the IUIS Expert Committee on IEI reports on 67 novel IEIs. These new gene defects bring the total number of IEIs to 559 resulting from variants in 508 genes[2].

Though PIDs are considered to be rare in the population, recent studies have shown that PIDs may be more common than previously estimated. The prevalence of PIDs varies depending on the type of immune-deficiencies and is difficult to be precisely calculated as the number of diagnosed cases is rapidly increasing. A 2018 global survey from the Jeffrey Modell Centers Network (JMCN) reported the case of PID patients followed in the JMCN had been increased[1]. Most of the cases reported are from developed countries. It is estimated that 70–90% of individuals living with a PID are undiagnosed [1], particularly in the area with poor medical condition and lacking laboratory resources. With the extensive application of exome or whole genome sequencing, it was predicted that the associated PID genetic defects would reach 1000 under current trend in next decade [1].

In 2020, published and unpublished studies of PID from January 1981 to June 2020 were systematically reviewed and summarized the currently available experiences from different countries regarding the registration and the prevalence of PID patients and emphasize the current burden of these diseases worldwide. This effort identified a total of 104614 registered patients and suggests identification of at least 10590 additional PID patients, mainly from countries located in Asia and Africa. A total of 15939 PID patients from 18 nationwide registries were surveyed in Asia and the first PID registry was reported in Japan[3].

Patients with PIDs present with highly heterogeneous clinical symptoms. Recurrent infection is the hallmark of the PIDs, however, noninfectious manifestations, such as gastrointestinal disorders, hematological diseases, autoimmune/autoinflammatory conditions, atopy or malignancy etc can be the predominant clinical presentations in some patients with underlying immunodeficiency[4,5]. Patients with PIDs also demonstrate overlapping symptoms and share similarities with many routine diseases[5].

An increased susceptibility to infection is the hallmark of the primary immunodeficiency diseases. Typically, the infections do not occur only in a single anatomic site, but usually involve multiple organs or multiple sites within the same person. Recurrent sinopulmonary infections, such as otitis, sinusitis, bronchitis, and pneumonia, are the most common presenting manifestations of the PIDs, but recurrent systemic infections such as bacteremia and meningitis are also seen[6].

Laboratory testing is essential for diagnosis and to delineate the immunologic defects of PIDs. Patient and family history along with physical examination are the first steps for further evaluation of laboratory investigations. The differentiation of PIDs from other medical conditions could be difficult. Hence, it is important to delineate the infectious organisms, the pattern of infections, and clinical pictures for guiding the clinical judgment, prior to focusing on laboratory testing [7]. Early diagnosis of PIDs is critical for reducing morbidity or mortality and improving treatment outcomes.

Unfortunately, delayed diagnosis of patients with PIDs is substantial, especially in developing countries which has an adverse effect on the patients' prognosis[8]. There is a paucity of data on the spectrum of PIDs from the developing world. The present study aimed to describe the clinical and laboratory profiles of patients with PIDs at a tertiary care hospital in Bangladesh.

Methods

It was a cross sectional study conducted in the Pediatric Rheumatology division of department of Pediatrics (Indoor and Pediatric Rheumatology follow up clinic) and department of Microbiology and Immunology, Bangladesh Medical University (BMU), Dhaka from Jan, 2023 to December, 2024. One hundred and forty three patients < 18 years who were suspected as cases of PIDs and fulfilled the suggestive features of PID were enrolled in the study by purposive sampling method. Any patient presented with ≥ 2 of the following 10 criteria was defined as suspected case of PIDs - patients having ≥ 4 new ear infection within 1 year, ≥ 2 sinus infection within 1 year, ≥ 2 attacks of pneumonia within 1 year, ≥ 2 deep seated infections including septicaemia within 1 year, persistent thrush in mouth or fungal infection on skin, recurrent deep skin or organ abscess, failure of an infant to gain weight, need for intravenous antibiotics to clear infections, 2 or more months on oral antibiotics with little effect and family history of primary immunodeficiency[10]. Specific PID types were identified following the clinical features and results of the investigations according to diagnostic criteria set up by the European Society of Immunodeficiency Disorders (ESID)[3].

Patients with secondary causes of immunodeficiency and with recurrent infections due to some other underlying diseases such as HIV infection, protein energy malnutrition, cystic fibrosis, malignancy, getting steroids, chemotherapy, ionizing radiation, chronic hypoxia etc were excluded from analysis. Ethical clearance was taken from Institutional Review Board of BSMMU. (BSMMU/2022/10371, Date 13-10-2022)

History and clinical examination findings related to the study were recorded in the predesigned data collection sheet. Laboratory evaluation included complete blood count with absolute and differentials count of white blood cells and platelet count. Measurement of serum immunoglobulin (IgG, IgA, IgM, and IgE), peripheral blood lymphocyte subsets including the basic panel of T-cell subset (CD3, CD4, CD8), B cell (CD19) and natural killer cell (CD56) by flowcytometry were done.

For immunophenotyping for analysis of lymphocytes, blood sample in a test tube containing EDTA was processed as soon as possible. Combination of measured fluorochrome-conjugated monoclonal antibodies was added. After few steps of incubation and centrifugation analysis was done on a pre calibrated flow cytometer. Serum IgG, IgM, IgA levels were determined by an automated Nephelometry analyzer and IgE level by Chemiluminescence as per manufacturer's instruction.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) where appropriate, while categorical variables were presented as frequencies and percentages. Comparisons between PID and non-PID groups were performed using Student's t-test or Mann–Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical variables, as appropriate. One-way ANOVA was used for comparison of laboratory parameters among different PID subtypes. Binary logistic regression analysis was performed to identify independent risk factors associated with primary immunodeficiency disorders, and results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value of < 0.05 was considered statistically significant.

As this was a hospital-based cross-sectional study including all eligible suspected PID cases during the study period (January 2023 to December 2024), formal sample size calculation was not performed. However, post hoc statistical power was considered acceptable based on the observed effect sizes and significant associations identified in regression analysis.

Result

In this study, 143 patients with suspected PIDs were found over a period of two years. Final diagnosis of PIDs could be reached in 69(48.2%) of patients. The median age of onset of symptoms was 6 months in PIDs cases which was lower than non PIDs, though not statistically significant. The mean age at diagnosis was 63.65±57.01 months, and the diagnosis lag was 46.83±31.27 months. History of consanguinity was found to be present in 4.3% of PIDs patients, and only one had positive family history (sibling) of PID. The study population comprised of 40 boys and 29 girls with a male-to-female ratio of 1.4:1. There was no significant difference between PIDs and non PIDs group.

Table 1: Distribution and Demographic Profiles of PID Cases according to Subtypes (n=69)

	PID cases	Age at onset (years) Mean ± SD	Gender Ratio M:F	Diagnostic Delay (years) Mean ± SD
1	**Immunodeficiency affecting cellular and humoral immunity (17, 24.6%)**			
	SCID (4, 5.9%)	1.2 ± 0.3	4:0	1.2 ± 0.7
	T-B+NK- (1) T-B-NK- (1)			
	T-B-NK+ (1) T-B+NK+ (1)			
	CID (13, 19.1%)	3.7 ± 1.3	1.6:1	1.4± 0.6
2	**Combined Immunodeficiencies with associated syndromic features (12, 17.4%)**			
	WAS (2, 2.9%)	6.9 ± 1.1	2:0	1.2± 0.5
	HIES (10, 14.7%)	5.5 ± 2.1	1:1.5	3.9 ± 1.6
3	**Predominantly antibody deficiency (30, 43.5%)**			
	Agammaglobulinemia (9, 13.3%)	4.1 ± 1.9	0:9	2.5 ± 1.4
	X-Linked Agammaglobulinemia (11, 16.2%)	3.8± 0.9	11:0	3.6 ± 1.2
	CVID (10, 14.7%)	8.8 ± 2.7	1:1	2.8 ± 0.3
4	**Congenital defects of phagocyte number and function (5, 7.2%)**			
	Severe Congenital Neutropenia (1, 1.5%)	8	M	4.5
	CGD (4,5.9%)	1.1 ± 0.4	4:0	2.5 ± 1.4
5	**Auto-inflammatory Disorder** (1,1.5%)			
	CANDLE syndrome (1, 1.5%)	5	F	3
6	**Complement Deficiency** (1, 1.5%)			
	Congenital C3 deficiency (1, 1.5%)	6	F	2
7	**Defects of Intrinsics and innate immunity (3, 4.4%)**			
	NK cell defect (3, 4.4%)	2.5 ± 1.4	1:2	2.6± 1.1

All PIDs cases were distributed in 12 diseases of seven main categories of PIDs (Table 1). Predominantly antibody deficiencies were the most common (43.5%). Within this category agammaglobulinemia was the most frequent subtype. Immunodeficiency affecting cellular and humoral immunity and combined immunodeficiency with associated syndromic features were also found in the series. The most common phenotype encountered in the category of immunodeficiency syndromes was Hyper IgE syndrome (HIEs) (14.7%). Severe combined immunodeficiency (SCID) (5.9%) and chronic granulomatous disease (CGD)(5.9%) were also diagnosed (Table 1). Among combined immunodeficiencies, age at onset of symptoms for SCID and CID patients were early (1.2 and 3.7 years respectively) in comparison to WAS and HIES (6.9 and 5.5 years respectively). Diagnostic delay was more in HIES patients (3.9 years). Male predominance was found in all 3 categories other than HIES (Table 1). Age of onset of symptoms for predominantly antibody deficiency group was little higher, and diagnostic delay was more than 2 years in all subtypes (Table 1).

Considering clinical manifestations, deep seated infections including septicemia was found in all the predominantly antibody deficiency subtypes, 23% of CIDs, 25% of CGDs, and in SCN patient. Recurrent deep skin/organ abscess was found in almost all the subtypes in the series except CVID and SCN. Persistent oral thrush was also present in all except WAS. Two or more episodes of pneumonia was observed in all patients except WAS and congenital C3 deficiency. Serious sinus infection was found mostly in few percentages of CID (46.1%) and agammaglobulinemia (44.4%) patients. Almost all patients had GIT infections except HIES. All patients in the series needed IV antibiotics to clear infection (Table 2).

Table 2: Clinical Manifestations of PIDs (n=69)

	PID cases	2 or more deep seated infections including septicemia	Recurrent deep skin/organ abscess	Persistent oral thrush	2 or more Pneu monia	2 or more serious sinus infection	4 or more ear infection	Need of IV antibiotics to clear infection	GIT infection	Others
1	**Immunodeficiency affecting cellular and humoral immunity (17)**									
	SCID (4)	-	2(50%)	3 (75%)	4(100%)	1(25%)	2(50%)	4 (100%)	1 (25%)	UTI (3,75%)
	CID (13)	3 (23%)	5(38.5%)	8 (61.5%)	13(100%)	6(46.1%)	4(30.8%)	13 (100%)	7 (53.9%)	UTI (6,46.1%) Septic arthritis (1,7.7%)
2	**Combined Immunodeficiencies with associated syndromic features (12)**									
	WAS (2)	-	2 (100%)	-	-	-	-	2(100%)	2(100%)	
	HIES (10)	-	10 (100%)	8(80%)	5(50%)	1(10%)	3(30%)	10(100%)		-
3	**Predominantly antibody deficiency (30)**									
	Agammaglobulinemia (9)	3(33.3%)	2(22.2%)	5 (55.6%)	9(100%)	4(44.4%)	2(22.2%)	9 (100%)	6(66.7%)	UTI(8,88.9%)
	X-Linked Agammaglobulinemia (11)	4 (36.4%)	3(27.3%)	9 (81.8%)	11(100%)	4(36.4%)	3(27.3%)	11(100%)	5 (45.5%)	UTI (8,72.7%) Meningitis (1, 9%)
	CVID (10)	1(10%)	-	4(40%)	8(80%)	-	1(10%)	10(100%)	5(50%)	-
4	**Congenital defects of phagocyte number and function (5)**									
	Severe Congenital Neutropenia (1)	1(100%)	-	1(100%)	1(100%)	-	-	1(100%)	1(100%)	UTI (1,100%)
	CGD (4)	1(25%)	2(50%)	3 (75%)	4(100%)	1(25%)	1(25%)	4 (100%)	4 (100%)	UTI (3,75%)
5	**Auto-inflammatory Disorder** (1)									
	CANDLE syndrome (1)	-	1(100%)	1(100%)	1(100%)	-	-	1(100%)	1(100%)	UTI (1,100%)
6	**Complement Deficiency** (1)									
	Congenital C3 deficiency (1)	-	1(100%)	1(100%)	-	-	-	1(100%)	1(100%)	UTI (1,100%)
7	**Defects of Intrinsics and innate immunity(3)**									
	NK cell defect (3)	-	1(33.3%)	3 (100%)	3 (100%)	-	-	3 (100%)	3(100%)	-

Total leukocyte count was markedly increased in CGD cases. The absolute lymphocyte count (ALC) was found to be low in cases of SCID, CID and SCN patients. The absolute neutrophil count was high in CGD and low in SCID, CID, WAS, HIES and SCN cases. Thrombocytopenia was observed in cases of WAS (Table 3).Total WBC count was significantly low in PIDs cases in comparison to non PIDs counterparts. Both differential and absolute Lymphocyte count werealso significantly low among PIDs cases. Immunoglobulin levels were lower in Combined and humoral immunodeficiencies in comparison to other varieties (Figure 1). All types of immunoglobulin levels were significantly low in PIDs cases in comparison to non PIDs patients.

Table 3: CBC findings in Different PID subtypes

	PID cases	TC of WBC (thousand/microliter) Mean ± SD	ANC(cells/microliter) Mean ± SD	ALC (cells/microliter) Mean ± SD	PC (lac/ microliter) Mean ± SD
1	**Immunodeficiency affecting cellular and humoral immunity (17)**				
	SCID (4)	1.8 ± 0.7	511 ± 117	2717 ± 117	4.05± 1.17
	CID (13)	4.2 ± 1.7	693± 70	2884± 276	3.87± 2.1
2	**Combined Immunodeficiencies with associated syndromic features (12)**				
	WAS (2)	7.9 ± 2.1	750 ± 120	4800± 1205	0.67 ± 0.11
	HIES (10)	10.8 ± 2.6	1018 ± 270	3435 ± 1605	3.34± 1.2
3	**Predominantly antibody deficiency (30)**				
	Agammaglobulinemia (9)	8.5 ± 1.9	4272 ± 1127	3507± 1425	2.95 ± 1.1
	X-Linked Agammaglobulinemia (11)	8.6± 2.2	4122± 813	3548 ± 1218	4.37±1.7
	CVID (10)	13.9 ± 4.7	6407 ± 2100	4061 ± 2803	2.83 ± 0.7
4	**Congenital defects of phagocyte number and function (5)**				
	Severe Congenital Neutropenia (1)	1.7	260 ± 17	1096	3.14
	CGD (4)	19.1 ± 2.4	10372 ±21 07	5632± 2514	2.40 ± 0.9
5	**Auto-inflammatory Disorder** (1)				
	CANDLE syndrome (1)	1.2	6780	3800	3.24
6	**Complement Deficiency** (1)				
	Congenital C3 deficiency (1)	9	7600	3600	4.15
7	**Defects of Intrinsics and innate immunity(3)**				
	NK cell defect (3)	7.5 ± 1.5	6352 ± 1203	3836± 2611	3.62 ± 1.9

CD3, CD4 and CD8 (% and absolute count) were low in all combined immunodeficiency cases except HIES. CD19+ CD27+IgD- were invariably low in almost all combined immunodeficiency subtypes. CD19+ cell count was low in all agammaglobulinemia cases. CD19+CD27+IgD- percentage was low in all predominantly antibody deficiency patients (Table 4). In logistic regression analysis, recurrent pneumonia, persistent oral thrush and need of IV antibiotics were the significant risk factors of developing PIDs (Table 6).

Table 4: Lymphocyte Subset Analysis in Different Immunodeficiency Cases (n=29+30)

Variables	Mean ± SD				P value	Mean ± SD		P value
	Combined Immunodeficiency (n=29)					Predominantly antibody Deficiency (n=30)		
	SCID(n=4)	CID(n=13)	WAS(n=2)	HIES(n=10)		Agammaglobulinemia (XLA and others) (n=20)	CVID (n=10)	
CD3+ T Cell (%)	28.3±8.1	50.6±45.8	30.7±12.5	47.8±32.8	0.703	65.8±21.1	71.4±14.9	0.19775
Absolute Count (cells/µl)	440.3±391.5	134.7±93.7	1162.4±390	1180.8±181.2	0.000	2806±424.3	2906±431.3	0.799348
CD4+ T cell (%)	23.4±11.0	25.3±13.7	27.8±4.7	50.8±17.6	0.000	25.3±18.4	19.6±7.1	0.21097
Absolute Count (cells/µl)	507.9±83.0	1120.4±250.7	1350±349.4	1810±120.6	0.000	464.1±80.9	490.9±116.2	0.045776
CD8+ T cell (%)	12.2±8.2	14.3±8.0	16.8±7.6	14.2±5.5	0.417	38.9± 14.4	12.7±8.2	0.28062
Absolute Count (cells/µ)	137±79.2	387.0±263	487±163.1	395±203.1	0.233	1235.8±146.2	496.5±29	0.427227
CD4+CD8+ratio	0.5±0.2	0.9±0.2	1±0.5	0.77±0.2	0.040	0.5±0.2	1.8±0.5	0.771932
CD 19+ B cell(%)	3.9±0.1	9.1±10.8	15.5±0.2	16.8±0.2	0.012	1.5±0.2	16.1±1.3	0.496463
Absolute Count(cells/µl)	258.1±116	352.5±50.2	186±66	3879±416	0.000	202.9±27.3	577±14.1	< 0.00001
CD56+ NK cell(%)	8.3±1.3	4.8±1.4	3.9±0.1	20.8±2.4	0.000	4.8 ± 2.3	4.7±1.7	0.451888
Absolute Count(cells/µl)	221.3±36.2	168.5±46	386±72.2	586.8±116	0.000	205.8± 79.6	94 ±50.9	0.141288
CD4+CD45RA+ (%)	42.0±16.3	46.5±5	94.3±18	44.3±8	0.000	90.8±9.2	49 ±12.7	0.030682
CD4+CD45RO+ (%)	58.9±0.2	43.5±5	4.16±0.09	8.26±1.0	0.000	4.1 ± 1.2	8±2.7	0.319224
CD8+CD45RA+ (%)	47.8±11.2	48.6±1 2.1	24.26±8.0	35.16±9.1	0.005	91.5 ± 12.1	38.5±2.1	0.000223
CD8+CD45RO+ (%)	6.0.±2.2	7.5±2.1	3.86±1.16	3.98±1.76	0.003	16.8 ± 2.28	21.5 ±2	0.361273
CD19+CD27+IgD- (%)	0.4±0.2	0.5±0.1	2.4±0.7	2.4±0.3	0.000	0.27 ±0.14	0.2 ±0.1	0.807183

Table 5: Treatment Modalities and Outcome of PID patients (n=69)

	PID cases	Treatment Modalities			Outcome	
		Anti-microbial prophylaxis n(%)	IVIG	Others	Stable	Expired
			n(%)	n(%)	n(%)	n(%)
1	**Immunodeficiency affecting cellular and humoral immunity (17)**					
	SCID (4)	4(100%)	4(100%)	-	-	4(100%)
	CID (13)	13(100%)	10(76.9%)	-	12(92.3%)	1(7.7%)
2	**Combined Immunodeficiencies with associated syndromic features (12)**					
	WAS (2)	2(100%)	2(100%)	Platelet transfusion -2(100%)	1(50%)	1(50%)
	HIES (10)	10(100%)	10(100%)	Bronchodilators10(100%) Montelukast – 10(100%)	10(100%)	-
3	**Predominantly antibody deficiency (30)**					
	Agammaglobulinemia (9)	9(100%)	9(100%)	-	8(88.9%)	1(11.1%)
	X-Linked Agammaglobulinemia (11)	11(100%)	1(100%)	-	10(91.0%)	1(9.0%)
	CVID (10)	10(100%)	8(80%)	Corticosteroid - 2(20%) Azathiprine – 1 (10%) Mycophenolate Mofetil – 1 (10%)	8(80%)	2(20%)
4	**Congenital defects of phagocyte number and function (5)**					
	Severe Congenital Neutropenia (1)	1(100%)	-	G-CSF- 1(100%) Corticosteroid – 1(100%)	-	1(100%)
	CGD (4)	4(100%)	-	-	4(100%)	-
5	**Auto-inflammatory Disorder** (1)					
	CANDLE syndrome (1)	1(100%)	1(100%)	Methotrexate – 1(100%) Corticosteroid - 1(100%) Baricitinib - 1(100%)	-	1(100%)
6	**Complement Deficiency** (1)					
	Congenital C3 deficiency (1)	1(100%)	-	Vaccination against capsulated organism 1(100%)	1(100%)	-
7	**Defects of Intrinsics and innate immunity(3)**					
	NK cell defect (3)	3(100%)	3(100%)	-	3(100%)	-

Almost all the patients of all subtypes received antimicrobial prophylaxis. Except patients of congenital defects of phagocyte number and function and congenital C3 deficiency, most of the patients of other subtypes of this cohort received IVIG periodically. No patients underwent hemopoeitic stem cell transplantation (Table 5). All the SCID and severe congenital neutropenia patients expired in the course of illness, rest of the patients were stable with the above mentioned management (Table5).

Table 6: Logistic Regression for Assessing Association between Primary Immune Deficiency and its Risk Factors

Variable	OR	95%CI	P value
Age	0.72	0.68-1.0	0.70
Male Gender	1.54	0.35 - 6.72	0.47
Consanguinity	1.08	0.24 - 3.18	0.92
Recurrent Pneumonia	2.64	1.17- 5.8	0.02
Need of IV antibiotics	3.3	2.22-9.31	0.03
Persistent oral thrush	2.49	1.68-6.8	0.02

OR: odds ratio; CI: confidence interval

Discussion

PIDs still remain underdiagnosed in developing part of the world. PIDs have a wide spectrum of clinical manifestations and laboratory findings. This study aimed to evaluate various types of PIDs based on clinical presentations and laboratory findings in our resource-limited setting to enhance awareness, share our results, and establish a patient registry for future research.

In this study, a total of 143 suspected PIDs were evaluated. Among them 69 (48.2%) were confirmed as PIDs. Mean age of PIDs cases and onset of infection were 63.65 ± 57.01 and 16.82 ± 26.47 months respectively. In a prospective study in Kolkata, 54% cases were male and 70% of cases were detected below one year age[11]. Another study done by Krishna et al. showed that 70% the PIDS patients in their pool had onset of symptoms before the age of 1 year[12]. In this study age of onset of symptom was around one year which coincides with above studies.

Males (57.4%) were affected predominantly which could be partly due to gender bias in seeking medical care. Male gender was predominant nearly in IEI reports around the globe specially in reports from Germany[13], ESID registry[14], and the MENA registry[15], the highest proportion was reported in Asian reports, namely in Korea[5,16] at 3.6:1 suggesting a greater prevalence of X-linked inheritance.

Diagnostic delay in PIDs refers to the time lag between the initial onset of symptoms and the formal diagnosis of the condition. This delay is a significant concern due to its potential to exacerbate the severity of the disease and lead to irreversible complications. In this study, diagnostic delay was 46.83 ± 31.27 months. In Iran, a cross-sectional study among 200 suspected PIDs patients observed that the mean diagnostic delay was 2.05 ± 1.7 years which is lower than our observation[17]. This could be due to varied and non-specific symptoms of PIDs, low awareness among healthcare professionals, resource constraints, lack of newborn screening programs etc.

In this study majority of the cases (43%) had antibody deficiency followed by immune-deficiencies affecting cellular and humoral immunity (24.63%). Other varieties included combined immunodeficiencies with associated syndromic features, congenital defects of phagocyte, NK cell defect, congenital C3 deficiency (Table 1). In a Bangladeshi study by Laila et al. it was also found that majority of PIDs were from antibody deficiency (40%) and combined immunodeficiency (32%) subtypes, followed by complement deficiencies, NK cell defect, and autoinflammatory disorders which is similar to the present study[18].

In 2020, published and unpublished studies from January 1981 to June 2020 were systematically reviewed, where a total of 15939 PID patients from 18 nationwide registries were surveyed in Asia[4]. Unlike ours, in Japanese registry, the most common PID subtype was autoinflammatory disorders (39%), followed by predominantly antibody deficiencies (14.4%), combined immunodeficiencies with syndromic features (8.7%), diseases of immune dysregulation (8.7%), congenital defects of phagocytes (7.9%), and combined immunodeficiencies (3.9%) [19]. In a total 3056 PID patients reported by the Iranian PID network centers, predominantly antibody deficiencies (29.5%) and combined immunodeficiency (17.3%) were the most common PID subcategories. SCID was reported as the most frequent specific disorder (21.1%) followed by CVID (14.9%)[15]. Both the studies have similarities with our findings. The predominantly antibody deficiency category ranked the highest percentage in Germany, Russia, South Africa, and Colombia[20].

Age at onset of symptoms were around one year in severe combined immunodeficiency disorder (SCID) patients which is the lowest, and highest in common variable immunodeficiency (CVID) patients which was around 8 years. Almost all SCID and XLA patients were male (Table 1). The variation of diagnostic delay between PIDs categories depended on severity of disease, timing of onset, and referral. The longest diagnostic delay mean was reported in severe congenital neutropenia patient followed by hyper IgE syndrome (4.5 years and 3.9 years respectively) case (Table 1).

In this study, suspicion of PIDs was done considering the ten warning signs proposed by the Jeffrey model foundation (JMF)[10]. Among 69 diagnosed PID cases almost 90% cases presented with failure to thrive, and needed IV antibiotics to clear infection. More than two third patients presented with two or more episodes of pneumonia. Around 30–40% of patients presented with four or more new ear infection, recurrent deep skin/organ abscess and persistent thrush in mouth. Deep seated infections including septicemia was found in all the predominantly antibody deficiency subtypes, 23% of CIDs, 25% of CGDs, and in SCN patient. Persistent oral thrush and recurrent pneumonia were found in almost all patients except WAS. Serious sinus infection was found mostly in few percentages of CID (46.1%) and agammaglobulinemia (44.4%) patients. Almost all patients had GIT infections except HIES. One CVID patient had non-Hodgkin lymphoma (Table 2).

Infections serve as the key hallmark signs for the presence of PIDs. In general, children with PIDs develop infections more frequently, severely, and more atypically[12]. Respiratory disorders are significant causes of morbidity and the leading causes of death (30% – 65%) in children with PIDs. The most common clinical manifestations are infections involving the respiratory tract, e.g. rhino-sinusitis, otitis media, bronchitis, bronchiectasis and recurrent pneumonia [21]. In a Bangladeshi study reported infections, especially infection of the respiratory tract (88%) and skin (84%), were the main features of PID[18]. Recent medical literature highlights growth failure as a persistent and significant non-infectious manifestation in Iranian children with Inborn Errors of Immunity (IEI). In the 2024–2026 reporting period, research emphasizes that immune dysregulation, chronic inflammation, and socio-economic challenges remain the primary drivers of growth impairment in this population[22]. Regarding individual PIDs, Heiba et al from Egypt found that pneumonia was the most common infection in patients with XLA (90.9%) and skin diseases like eczema were frequent in them (63.6%)[23]. Our findings concurred with those of previous research projects carried out both domestically and outside.

In current study, there was a significant decrease in leukocyte count, lymphocyte percentage and serum immunoglobulin level in PIDs cases in comparison to non PIDs. Total leukocyte count and absolute neutrophil count were markedly increased in CGD cases. The absolute lymphocyte count (ALC) was found to be low in cases of SCID, CID and SCN patients. Thrombocytopenia was observed in cases of WAS (Table 3). A Complete Blood Count (CBC) is an essential initial test for diagnosing PIDs in children, revealing abnormalities like lymphopenia in T-cell disorders, neutropenia in phagocytic defects, or thrombocytopenia in conditions like Wiskott-Aldrich syndrome. While a normal CBC often rules out T-cell related defects, the CBC's value lies in guiding further specialized testing rather than providing a definitive diagnosis on its own, requiring age-specific interpretation of cell levels in children[24].

Suspected PIDs should be evaluated in a stepwise fashion, with initial, nonspecific testing that includes measurement of total serum immunoglobulin and evaluation of antibody titers. Abnormal test results may suggest allergy, immunodeficiency, or chronic illness and should prompt further testing, which might include lymphocyte subset analysis by flow cytometry and IgG subclass testing. In this study, all types of immunoglobulin levels were significantly low in PIDs cases in comparison to non PIDs patients. Immunoglobulin levels were lower in Combined and humoral immunodeficiencies in comparison to other varieties (Fig. 1).

Regarding lymphocyte subset analysis, in combined immunodeficiency group CD3+, CD4+, CD8 + T cells and CD19 + B cells absolute count were decreased. Total lymphocyte count and T cells subsets were significantly low in all SCID cases (Table 4). In a cross sectional study in Pakistan, 60 PIDs cases were evaluated where there was significant reduction of T lymphocytes in combined immunodeficiency group in comparison to humoral immunodeficiency [25].Ogulur et al. found all CVID patients with pediatric onset had decreased levels of total and memory B cells, CD4 + T cells, CD4 + CD45RA+ naive T cells which support our findings[24]. So, flow cytometry has emerged as a highly valuable and cost effective tool for diagnosing and studying most PIDs, particularly in low-income countries where access to genetic testing can be limited.

In this study, some risk factors had been identified associated with PIDs such as recurrent pneumonia, need of IV antibiotics, persistent oral thrush (Table 6). In 2013, recent cohort and predictive-model studies (2025–2026) demonstrate that the most significant predictors of IEI in children include recurrent severe infections, failure to thrive, positive family history, and need for intravenous antibiotics, while laboratory markers such as lymphopenia, hypogammaglobulinemia, and low IgE further improve diagnostic accuracy. Emerging evidence also highlights immune dysregulation and autoimmune manifestations as important predictors.[26,27,28].

As PIDs consist of a wide variety of disorders, appropriate diagnosis is very important for appropriate treatment. The treatment options for IEIs are antimicrobial prophylaxis, Immunoglobulin replacement therapy (IGRT), allogeneic hematopoietic stem cell transplantation (HSCT), and gene therapy (GT)[29]. In this panel, all the patients received antimicrobial prophylaxis, and most of them received IVIG periodically (Table 5). No patients underwent hemopoeitic stem cell transplantation or gene therapy due to resource limited set up.

According to the the European Society for Immunodeficiencies patient registry (ESID-R) report, the highest number and proportion of IGRT-receiving patients were seen in predominantly antibody deficiency patients which is nearly similar to this study. Unlike ours, IGRT and HSCT were documented in patients with IEI/PID in any category, and GT was recorded in a descending order for CID, syndromic, and phagocyte disorders. [30].

The survival probabilities of patients in the 10 IUIS categories differ due to their varying predispositions to life-threatening infections, malignancies, autoimmunity, or other manifestations and complications associated with their underlying conditions. Here in this cohort all the SCID and severe congenital neutropenia patients expired in the course of illness, rest of the patients were stable with the above mentioned management (Table 7).

Conclusion

The present study reports findings from clinical observations of 69 patients diagnosed with primary immunodeficiencies (PIDs). The results indicate significant disease patterns, including frequent respiratory infections, autoimmune manifestations, and recurrent fevers, as well as specific clinical presentations, diagnostic delays, essential laboratory assessments, treatment protocols, and immediate outcomes. These findings would be helpful to physicians and researchers relevant to patient care, management, and policy-making for PID patients in the country.

Abbreviations

ALC – Absolute Lymphocyte Count

BMU – Bangladesh Medical University

BSMMU – Bangabandhu Sheikh Mujib Medical University

BTK – Bruton Tyrosine Kinase

CBC – Complete Blood Count

CD – Cluster of Differentiation

CGD – Chronic Granulomatous Disease

CID – Combined Immunodeficiency

CVID – Common Variable Immunodeficiency

DHR – Dihydrorhodamine Assay

DOCK8 – Dedicator of Cytokinesis 8

EDTA – Ethylenediaminetetraacetic Acid

ESID – European Society of Immunodeficiency Disorders

GIT – Gastrointestinal Tract

GT – Gene Therapy

HIES – Hyper IgE Syndrome

HIV – Human Immunodeficiency Virus

HSCT – Hematopoietic Stem Cell Transplantation

IEI – Inborn Errors of Immunity

IgA – Immunoglobulin A

IgE – Immunoglobulin E

IgG – Immunoglobulin G

IgM – Immunoglobulin M

IGRT – Immunoglobulin Replacement Therapy

IUIS – International Union of Immunological Societies

IV – Intravenous

IVIG – Intravenous Immunoglobulin

JMCN – Jeffrey Modell Centers Network

JMF – Jeffrey Modell Foundation

MENA – Middle East and North Africa

NBT – Nitroblue Tetrazolium Test

NHL – Non-Hodgkin Lymphoma

NK – Natural Killer

PID – Primary Immunodeficiency Disorder

PIDs – Primary Immunodeficiency Disorders

SCID – Severe Combined Immunodeficiency

SCN – Severe Congenital Neutropenia

SPSS – Statistical Package for the Social Sciences

IV – Intravenous

WAS – Wiskott-Aldrich Syndrome

WBC – White Blood Cell

XLA – X-linked Agammaglobulinemia

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University under approval number BSMMU/2022/10371 dated 13-10-2022. The study was conducted in accordance with institutional ethical standards and the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participating children prior to enrollment. Confidentiality of patient information was strictly maintained throughout the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests related to this study. No financial or non-financial conflicts of interest influenced the design, conduct, analysis, or reporting of this research.

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Authors' contributions

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HAM: Methodology, Resources, Visualization, Supervision, Validation, Visualization

MH: Resources, Visualization, Writing – review & editing.

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Table

Table 7 is not available with this version.

Figures

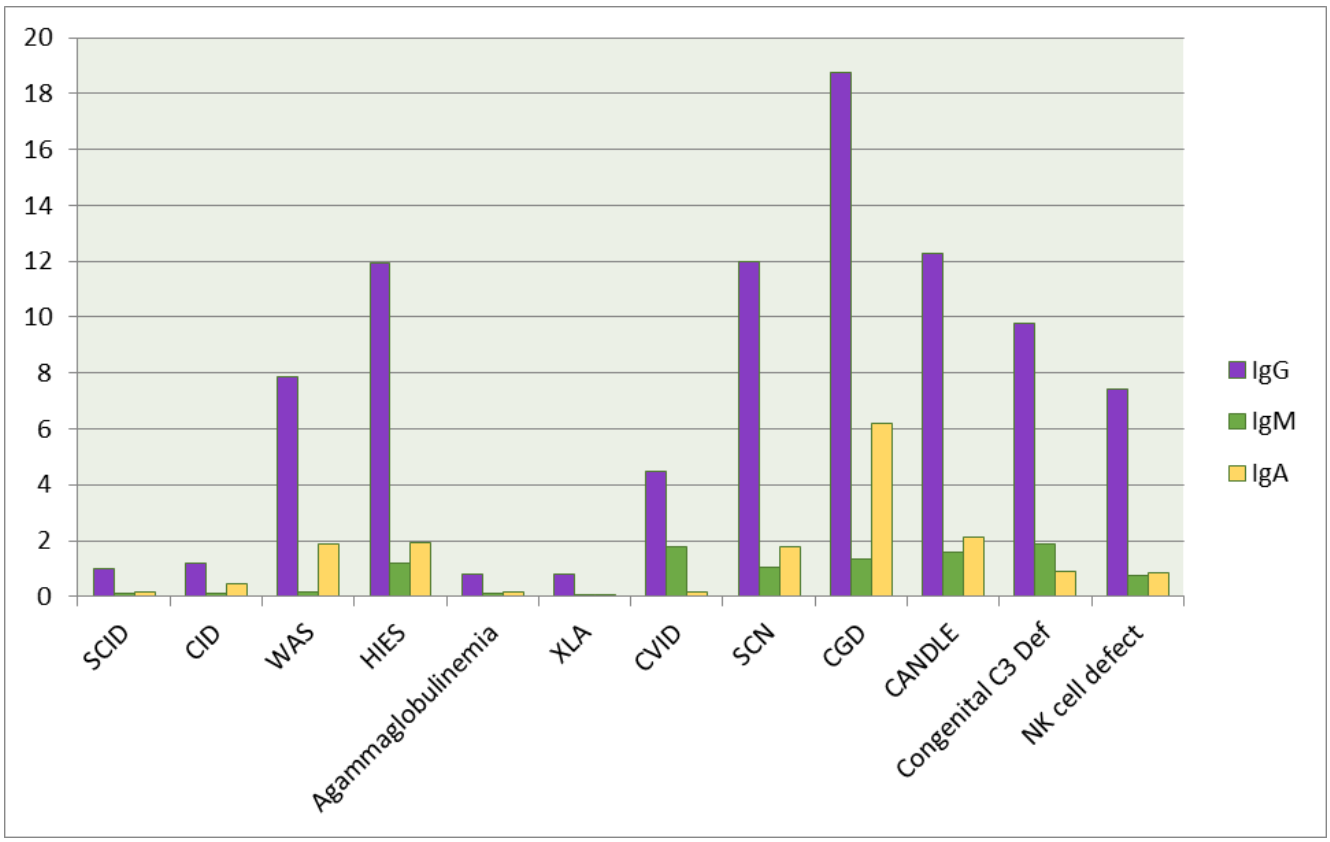


Figure 1

Serum Immunoglobulin Profile in suspected PID patients (n=69)