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# Clinical and Immunological Spectrum of Adult Patients Evaluated for Suspected Inborn Errors of Immunity: Insights from a Tertiary Immunology Center

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## ABSTRACT

**Objective:** Inborn errors of immunity (IEI) represent a heterogeneous and expanding group of disorders with a broad clinical spectrum extending beyond recurrent infections. This study aimed to evaluate the demographic, clinical, and immunological characteristics of adult patients referred with suspicion of IEI.

**Materials and Methods:** In this single-center retrospective observational study, the medical records of 433 patients referred to the Immunology and Allergy outpatient clinic between January 2021 and December 2022 with symptoms suggestive of IEI were retrospectively reviewed.

**Results:** The most common presenting complaints were frequent respiratory tract infections, skin/mucosa findings like delayed wound healing or oral aphthous ulcers, family history of IEI, diarrhea, uncontrolled severe asthma, and frequent urinary tract infections. Decreased serum IgG, IgM, and IgA levels were observed in 11.3% (n=49), 10.4% (n=45), and 14.1% (n=61) of the patients, respectively. Reduced IgG subclass levels were detected as follows: IgG1 in 6.7% (n=29), IgG2 in 10.6% (n=46), IgG3 in 3.7% (n=16), and IgG4 in 6% (n=26). Flow cytometric analysis revealed decreased $CD19^+$ B cell counts in 20.3% (n=88), $CD4^+$ T cell counts in 10.4% (n=45), $CD8^+$ T cell counts in 6.9% (n=30), $CD16^+$ natural killer (NK) cell counts in 15.2% (n=66), and $CD56^+$ NK cell counts in 11.1% (n=48) of the patients. Selective IgA deficiency was identified in 24 patients, selective IgM deficiency in 15, IgG subclass deficiency in 22, and isolated IgG deficiency in 20 patients. Following comprehensive immunological evaluation, 21 of the 433 patients (4.8%) were newly diagnosed with IEI and immunoglobulin replacement therapy was initiated.

**Conclusion:** Although most patients presenting with signs suggestive of immune dysfunction do not ultimately receive a diagnosis of IEI, a meaningful proportion can still be identified through appropriate immunological evaluation. These findings emphasize the importance of interpreting laboratory abnormalities together with both infectious and non-infectious clinical manifestations in the diagnostic assessment of suspected immunodeficiency.

**Keywords:** Autoimmunity, inborn errors of immunity, infection, malignancy, primary immunodeficiency

## INTRODUCTION

Primary immunodeficiencies (PIDs) are a heterogeneous and growing group of disorders caused by defects in the development or function of the immune system (1). They are now often called inborn errors of immunity (IEI) and are classified into 10 groups based on the components of the innate and adaptive immune responses affected. According to the latest update from the International Union of Immunological Societies (IUIS), 67 new mutations have been added, bringing the total to 508 distinct monogenic defects (2).

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Recurrent or severe infections are the most common clinical manifestations of IEI, particularly involving the respiratory tract (3). However, non-infectious manifestations such as autoimmune diseases, autoinflammation, unexplained cytopenias, allergies, lymphoproliferation, enteropathy, and malignancy may also represent important clinical clues (2-5). Because these findings are frequently encountered in routine clinical practice and are not specific to immunodeficiency, delays in diagnosis are common in IEI (6). Furthermore, the classical warning signs are not always adequate for the diagnosis (7).

Inborn errors of immunity can appear at any age but adults are more likely to experience longer delays in diagnosis than pediatric populations (4,6). Early recognition of patients with suspected immunodeficiency is essential to prevent complications, and increased morbidity and mortality (6). Therefore, evaluating patients who show clinical signs of immune dysfunction remains a key responsibility in immunology and allergy outpatient clinics. The aim of this study was to evaluate the demographic, clinical, and immunological characteristics of adult patients referred with suspicion of IEI.

## MATERIALS and METHODS

### Study Design and Population

This single-center, retrospective, observational, and descriptive study was approved by the Ethics Committee of our hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All participants included in the study were 18 years of age or older. The medical records of patients referred to the Immunology and Allergy outpatient clinic between January 2021 and December 2022 with symptoms raising suspicion for IEI were retrospectively reviewed. Demographic characteristics, clinical features, radiological findings, and laboratory parameters were evaluated through detailed chart review. Patients who had been previously diagnosed with IEI and were already receiving immunoglobulin replacement therapy (IgRT) at the time of referral were excluded from the study.

To assess the potential progression to IEI, patients with a prior diagnosis of selective IgA deficiency (sIgAD), and a patient with Hyper-IgE syndrome not receiving immunoglobulin replacement therapy (IgRT), were not excluded from the study. While the distinction between primary and secondary immunodeficiency is debated and Good syndrome is generally regarded as a secondary immunodeficiency, we did not exclude our patient diagnosed with Good syndrome, as it is classified among the phenocopies of IEI in the IUIS classification (2). The diagnosis of common variable immunodeficiency (CVID) in newly diagnosed patients was established based on the criteria defined by the European Society for Immunodeficiencies (ESID). For other IEI diagnoses, including selective antibody deficiencies, we also relied on the ESID Registry – Working Definitions for Clinical Diagnosis. Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) deficiency was diagnosed in one patient based on genetic testing results.

### Statistical Analysis

The data analysis of the study was performed using the IBM SPSS version 25.0 software. Descriptive statistics for continuous variables were presented as mean ± standard deviation (mean±SD), median, 1st quartile, 3rd quartile, and the minimum and maximum values. Categorical variables were expressed as counts and percentages. The normality of the data distribution was assessed using the Shapiro-Wilk test. Comparisons between categorical variables were assessed using the Pearson chi-square test, and Fisher's Exact and Exact chi-square tests were used when necessary. A significance level of $p<0.05$ was considered statistically significant.

## RESULTS

A total of 433 patients were included in the study, of whom 61.7% were female. The median age was 38 years (min.-max.;18-79). The most common presenting complaints were frequent upper respiratory tract infections, pulmonary infections, skin and mucosa findings like delayed wound healing or oral aphthous ulcers, family history of IEI, diarrhea, uncontrolled severe asthma, frequent urinary tract infections, and viral or fungal infections (Table I).

Allergic diseases constituted the most common comorbid conditions, including allergic rhinitis, chronic spontaneous urticaria, drug allergy, and bee venom allergy. Additional comorbidities included asthma, rheumatologic diseases, and Hashimoto's thyroiditis. Twelve patients had a prior diagnosis of sIgAD, and two patients had been previously diagnosed with Hyper-IgE syndrome. Radiological assessment demonstrated bronchiectasis in 29 patients (6.7%), hepatomegaly in 14 (3.2%), splenomegaly in 9 (2%), and lymphadenopathy in 8 (1.8%) (Table I).

The laboratory and immunological characteristics of all patients are presented in Table II. Low IgG, IgM, and IgA levels were observed in 11.3% (n=49), 10.4% (n=45), and 14.1% (n=61) of the patients, respectively. Decreased IgG subclass levels were detected as follows: IgG1 in 6.7% (n=29), IgG2 in 10.6% (n=46), IgG3 in 3.7% (n=16), and IgG4 in 6% (n=26). Serum IgE levels were found to be low in 22 patients (5.1%), whereas markedly elevated levels (>2000 IU/mL) were detected in 9 patients (2.1%).

Flow cytometric analysis revealed decreased $CD19^+$ B cell counts in 20.3% of the patients (n=88), decreased $CD4^+$ T cell counts in 10.4% (n=45), decreased $CD8^+$ T cell counts in 6.9% (n=30), decreased $CD16^+$ natural killer (NK) cell counts in 15.2% (n=66), and decreased $CD56^+$ NK cell counts in 11.1% (n=48) (Table II).

We classified the patients into six groups according to clinical conditions commonly observed in IEI and evaluated their associations with decreased immune parameters. Decreased CD19, CD16, IgA, IgG, and IgG2 levels were more frequent in patients with recurrent infections; decreased CD19, IgM, and IgA levels in those with autoimmunity; decreased CD19 and CD16 levels in patients with respiratory symptoms; decreased CD4, CD19, CD16, and CD56 levels in patients with malignancy; and decreased CD19 and CD16 levels in those with cutaneous/mucosal manifestations (Figure 1).

**Table I: Baseline characteristics of the study population.**

| | Patients (n=433) |
|---|---|
| Age in years, median ($Q_1$-$Q_3$) | 38 (27-48.5) |
| Female, n (%) | 267 (61.7) |
| Symptoms, n (%) | |
| Upper respiratory tract infections | 166 (38.3) |
| Pulmonary infections | 82 (18.9) |
| Autoimmunity | 66 (15.2) |
| Delayed wound healing | 47 (10.9) |
| Viral infections | 32 (7.4) |
| Family history of IEI | 29 (6.7) |
| Diarrhea | 24 (5.5) |
| Uncontrolled severe asthma | 22 (5.1) |
| Fungal infections | 19 (4.4) |
| Urinary tract infections | 19 (4.4) |
| Oral aphthous ulcers | 18 (4.2) |
| Weight loss | 6 (1.4) |
| Lymphadenopathy | 5 (1.2) |
| Spontaneous abortion | 5 (1.2) |
| Infertility | 5 (1.2) |
| Unusual infection | 4 (0.9) |
| Comorbidities, n (%) | |
| Allergic diseases | 64 (14.8) |
| Asthma | 50 (11.6) |
| Rheumatological pathology | 33 (7.3) |
| Hashimoto's thyroiditis | 29 (6.7) |
| Hypertension | 24 (5.5) |
| Diabetes mellitus | 22 (5.1) |
| Malignancy | 21 (4.9) |
| Skin pathology | 16 (10.2) |
| Cytopenia | 15 (3.4) |
| GIS pathology | 14 (3.2) |
| Selective IgA Deficiency | 12 (2.8) |
| Radiological findings, n (%) | |
| Bronchiectasis | 29 (6.7) |
| Hepatomegaly | 14 (3.2) |
| Splenomegaly | 9 (2) |
| Lymphadenopathy | 8 (1.8) |
| Pleural effusion | 9 (2.1) |

**GIS:** Gastrointestinal system, **IEI:** Inborn errors of immunity, **Ig:** Immunoglobulin

**Table II: The laboratory and immunological characteristics of the patients.**

| | Patients (n=433) |
|---|---|
| Leukocytes (x$10^3$ cells/uL), median ($Q_1$-$Q_3$) | 6.7 (5.5-8.3) |
| Hemoglobin (g/dL), median ($Q_1$-$Q_3$) | 13.6 (12.7-14.9) |
| Platelet (x$10^3$ cells/uL), median ($Q_1$-$Q_3$) | 256 (216-299.5) |
| Neutrophils (x$10^3$ cells/uL), median ($Q_1$-$Q_3$) | 4 (3.1-5.1) |
| Lymphocytes (x$10^3$ cells/uL), median ($Q_1$-$Q_3$) | 1.9 (1.6-2.4) |
| IgG (mg/dL), mean±SD | 1023.2 ± 292 |
| IgM (mg/dL), median ($Q_1$- $Q_3$) | 94 (67-139) |
| IgA (mg/dL), median ($Q_1$- $Q_3$) | 165 (101-226) |
| IgG1 (g/L), median ($Q_1$- $Q_3$) | 6.8 (5.5-8.1) |
| IgG2 (g/L), median ($Q_1$- $Q_3$) | 3.2 (2.4-4.1) |
| IgG3 (g/L), median ($Q_1$- $Q_3$) | 0.4 (0.3-0.5) |
| IgG4 (g/L), median ($Q_1$- $Q_3$) | 0.5 (0.2-0.9) |
| CD19 (%), median ($Q_1$- $Q_3$) | 10.1 (7.5-13.6) |
| CD4 (%), median ($Q_1$- $Q_3$) | 44 (39-50.8) |
| CD8 (%), median ($Q_1$- $Q_3$) | 30.7 (24.6-37) |
| CD16 (%), median ($Q_1$- $Q_3$) | 11.5 (7.8-17) |
| CD56 (%), median ($Q_1$- $Q_3$) | 12.5 (8.7-17.8) |
| CD3 (%), median ($Q_1$- $Q_3$) | 76.4 (71-81.2) |
| C3 (%), median ($Q_1$- $Q_3$) | 131.5 (115-144) |
| C4 (%), mean±SD | 30.8±9 |
| ESR (mm/h), median ($Q_1$-$Q_3$) | 15 (8-26.2) |
| CRP (mg/L), median ($Q_1$-$Q_3$) | 3 (1-8) |
| Vitamin D, median ($Q_1$-$Q_3$) | 22.4 (13.5-33.7) |

**CD:** Cluster of differentiation, **CRP:** C-reactive protein, **ESR:** Erythrocyte sedimentation rate, **Ig:** Immunoglobulin, **SD:** Standard deviation

A total of 24 patients were found to have sIgAD, 15 had selective IgM deficiency (sIgMD), 22 had IgG subclass deficiency, and 20 had only IgG deficiency. Following a comprehensive immunological evaluation, 21 of the 433 patients (4.8%) were newly diagnosed with IEI and IgRT was initiated in these patients. Of the newly diagnosed cases, 19 patients were diagnosed with CVID, while one patient each was diagnosed with CTLA-4 deficiency and Good's syndrome. Notably, one of the patients diagnosed with CVID had a previous diagnosis of sIgAD.

Among the remaining 11 patients with a history of sIgAD, immunological evaluation revealed low IgG4 levels in four patients, low IgG1 and IgG2 levels in one patient each, decreased CD19 levels in three patients, and decreased CD4 and CD8 levels in one patient each.

Of the 21 patients with newly diagnosed IEI, 76% presented with infections, while 33% exhibited autoimmune manifestations at presentation. Four patients presented with infections only, two with autoimmune manifestations only, one with isolated diarrhea, and one with isolated lymphadenopathy. Additionally, one patient was referred to our outpatient clinic because of severe/uncontrolled asthma without a history of recurrent respiratory tract infections. Weight loss and malignancy were also among the presenting complaints in two patients each. Radiological examinations of the 21 patients revealed splenomegaly in 9 patients, bronchiectasis in 8, hepatomegaly in 6, and lymphadenopathy in 2 (Table III).

## DISCUSSION

In our study, 4.8% of adult patients referred for immunological evaluation due to clinical suspicion over a 2-year period were diagnosed with IEI, and IgRT was initiated. However, a considerable proportion of patients without an indication for IgRT demonstrated diverse immunological abnormalities, including immunoglobulin deficiencies and alterations in lymphocyte subsets. These findings suggest that patients presenting with clinical features suspicious for immunodeficiency may represent a heterogeneous group with varying degrees of immune dysfunction.

Inborn errors of immunity may manifest later in life and can demonstrate a variable clinical course over time (2-6). In particular, sIgAD and CVID are the most frequently observed immunodeficiencies in adulthood, and

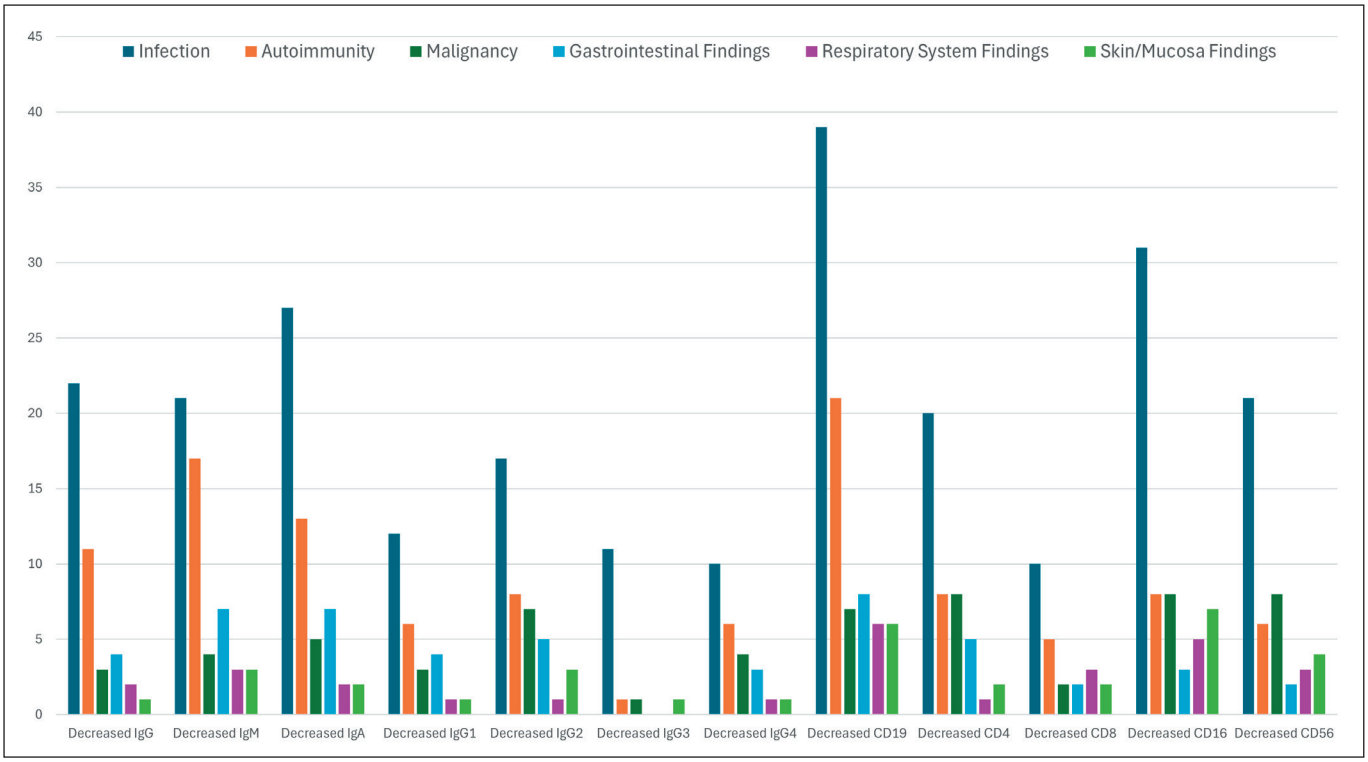


**Figure 1:** Common clinical conditions observed in inborn errors of immunity and their associations with decreased immune parameters in the study population.

**Table III: Baseline characteristics of the newly diagnosed IEI patients.**

| | Patients (n=21) |
|---|---|
| Age in years, mean±SD | 43.1±15.1 |
| Male, n (%) | 15 (71.4) |
| Symptoms, n (%) | |
| Infections | 16 (76) |
| Autoimmunity | 7 (33) |
| Diarrhea | 2 (9.5) |
| Weight loss | 2 (9.5) |
| Hemoptysis | 2 (9.5) |
| Lymphadenopathy | 2 (9.5) |
| Malignancy | 2 (9.5) |
| Uncontrolled severe asthma | 1 (4.8) |
| Allergic diseases | 1 (4.8) |
| Oral aphthous ulcers | 1 (4.8) |
| Infections alone | 4 (19) |
| Autoimmunity alone | 2 (9.5) |
| Diarrhea alone | 1 (4.8) |
| Lymphadenopathy alone | 1 (4.8) |
| Radiological findings, n (%) | |
| Bronchiectasis | 8 (38.1) |
| Hepatomegaly | 6 (28.6) |
| Splenomegaly | 9 (42.9) |
| Lymphadenopathy | 2 (9.5) |

**IEI:** Inborn errors of immunity, **SD:** Standard deviation

progression from sIgAD to CVID has been reported in a subset of patients (8-10). Similarly, in our cohort, one patient with a previous diagnosis of sIgAD was subsequently diagnosed with CVID. The predominant clinical manifestations in this patient were autoimmune cytopenia and recurrent upper respiratory tract infections. In this regard, the presence of isolated immunological abnormalities in patients without a definitive diagnosis of IEI at initial evaluation may reflect an early or evolving stage of immune dysfunction. Therefore, considering the potential for progression to clinically significant immunodeficiency over time in some patients, regular follow-up and raising awareness about this possibility are important.

The prevalence of sIgAD ranges from approximately 1/142 to 1/965, depending on the ethnicity (9-11). In Turkiye, the prevalence of sIgAD has been reported as 1:188 (0.52%) among healthy school-aged children in a nationwide study (12). Most patients remain asymptomatic; however, a subset may present with pulmonary infections, gastrointestinal disorders, autoimmune disease, allergic diseases, or malignancies (9-11,13). Notably, sIgAD was identified in 24 out of 433 patients (5.5%) in our cohort. This proportion is higher than that reported in the general population, which is expected given that our study population consisted of symptomatic individuals referred for immunological assessment. These findings underscore the importance of considering sIgAD in adults presenting with recurrent infections or autoimmune features.

Despite existing controversies about the definition of sIgMD, it is commonly defined as decreased IgM levels accompanied by normal IgG and IgA levels, without evidence of T-cell dysfunction (14,15). The reported prevalence ranges from 0.07% to 2.1%, depending on the population studied (16). In Turkiye, a retrospective study from Hacettepe University involving the review of the medical records of 27,000 pediatric patients, the prevalence was reported as 0.12% (17). Clinically, sIgMD is usually asymptomatic or presents with recurrent infections, and more rarely with autoimmune diseases, allergic disorders, and malignancies (16,17). In our study, 15 of 433 patients (3.4%) were found to have sIgMD, again exceeding population-based estimates and likely reflecting the selected nature of adults referred for immunologic evaluation. Our findings emphasize that sIgMD should not be overlooked in patients presenting with the signs of immunodeficiency.

IgG subclass deficiency is defined as a decrease in the serum concentration of one or more IgG subclasses while the total IgG concentration is normal (14). IgG subclass deficiency is not always associated with clinical disease and may be regarded as a laboratory abnormality. Clinically significant IgG subclass deficiency is defined by recurrent infections accompanied by a defective functional antibody response. Most individuals with a deficiency in one or more IgG subclasses are asymptomatic. In symptomatic patients, recurrent sinopulmonary infections are the predominant manifestation (18). IgG subclass deficiency was detected in 22 of 433 patients (5.1%) referred for suspected immunodeficiency in our patient group. This finding suggests that IgG subclass deficiencies are relatively frequent among adults undergoing immunological evaluation.

A notable finding of our study was that, among patients newly diagnosed with IEI, five presented primarily with non-infectious manifestations. As stated in previous studies, autoimmune disorders, enteropathy, and lymphoproliferation were among these findings (19,20). Interestingly, in one of these patients, uncontrolled severe asthma constituted the leading clinical presentation, and treatment with a biological agent was initiated alongside IgRT.

It was also noteworthy that hemoptysis was the presenting symptom of pneumonia in two of our patients. This observation highlights the importance of increasing awareness of the diverse clinical presentations of IEI, including severe asthma. Additionally, from another perspective, the identification of IEI in 8 of the 29 patients with bronchiectasis in our overall study population is also remarkable. To summarize, diarrhea, weight loss, severe/uncontrolled asthma, skin/mucosa findings, autoimmunity, malignancy, lymphadenopathy, bronchiectasis, and organomegaly are the clinical findings besides infections that may raise awareness among clinicians regarding an underlying immunodeficiency.

Given that the clinical manifestations of IEI in adults are often heterogeneous and nonspecific, diagnosis may be delayed or overlooked. The reported duration of diagnostic delay differs among studies, but recent evidence suggests that this interval has shortened over time (6). While the diagnostic delay in Europe has been reported to be approximately 4–5 years, studies from Turkiye indicate that this interval exceeds 10 years (21-23). The median diagnostic delay among patients newly diagnosed with IEI in our study was 3 years (range: 0–30). As highlighted in recent studies, this may stem from an inadequate level of awareness regarding IEI (24,25). Timely evaluation of patients with suspected immunodeficiency remains essential for early diagnosis and prevention of long-term complications. Our findings may aid in defining the potential clinical presentations of suspected immunodeficiency, promoting greater awareness and potentially shortening the time to diagnosis.

In our study group, decreased CD19 levels were observed in three patients, while decreased CD4 and CD8 levels were detected in one patient each, among the remaining 11 patients with a history of sIgAD other than the patient diagnosed with CVID. In a study involving detailed analysis of lymphocyte subsets in 30 patients with sIgAD, no decrease in CD19 or CD8 levels was observed, whereas decreased CD4 levels were reported in two patients. However, the same study reported significant decreases in marginal zone-like and switched memory B cells, as well as in central and effector memory $CD8^+$ T cell subsets and naïve and central memory $CD4^+$ T cell subsets (26). We also identified IgG subclass deficiencies in six of the 11 patients, consistent with the existing literature (27).

The retrospective and single-center design is the primary limitation of the current study. Predefined screening tools such as immunodeficiency warning signs were not used as strict inclusion criteria, as one of the aims of this study was to explore the broader spectrum of clinical presentations that may raise suspicion for immunodeficiency in routine clinical practice. Another limitation of our study is the lack of certain advanced immunological investigations such as molecular genetic studies, neutrophil oxidative burst assays, switched memory B cell analysis, and specific antibody responses. Although longitudinal follow-up was available for a subset of patients, longer-term prospective monitoring would be necessary to better define the natural history, selective immunoglobulin deficiencies, and progression risk of these abnormalities.

In conclusion, this study describes the cross-sectional characteristics of patients referred to an immunology and allergy outpatient clinic with findings suggestive of immunodeficiency, as well as those who were newly diagnosed with IEI and required IgRT during the evaluation process. We observed various immunological abnormalities in a considerable proportion of our patient group, but only 21 of 433 patients (4.8%) ultimately fulfilled diagnostic criteria for a defined IEI and required IgRT. In addition, a notable proportion were found to have selective antibody deficiencies. These findings highlight that although the majority of patients presenting with signs suggestive of immune dysfunction may not ultimately receive a diagnosis of IEI, a meaningful proportion can still be identified through appropriate immunological evaluation**,** emphasizing the importance of interpreting laboratory findings together with both infectious and non-infectious clinical manifestations. Also, close clinical and immunological follow-up of these immunological abnormalities is important to monitor for potential progression to a well-defined immunodeficiency over time.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**Ethics Statement**

This study was approved by the Gulhane Scientific Research Ethics Committee of the University of Health Sciences (2024/34).

**Author Contributions**

Concept: **MII, YAB,** Design: **MII,** Data collection or processing: **MII, YAB, FK, ES, OU, FD,** Analysis or Interpretation: **MII, OK,** Literature search: **MII, FD, SY,** Writing: **MII,** Approval: **MII, SY, OK.**

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