Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
www.all-imm.com

ORIGINAL ARTICLE

OPEN ACCESS

Primary immunodeficiencies: Clinical spectrum and follow-up challenges

Yasemin Akgul Balaban*, Mustafa Ilker Inan, Fikriye Kalkan, Ezgi Sonmez, Fevzi Demirel, Ali Selcuk, Sait Yesillik, Ozgur Kartal

Department of Immunology and Allergic Diseases, Ankara Gulhane Training and Research Hospital, Ankara, Turkey

Received 29 September 2025; Accepted 7 January 2026
Available online 1 May 2026

KEYWORDS
Cancer;
Common Variable Immunodeficiency;
Immunoglobulin Replacement Therapy;
Intravenous immunoglobulins;
Subcutaneous Immunoglobulins

Abstract
Primary immunodeficiencies (PIDs) are a rare group of diseases with a broad clinical spectrum. Patients usually present with infections; they may also present with autoimmunity, lymphoproliferative disorders, and/or cancers or these comorbidities may occur during the disease. We aimed to analyze the demographic and clinical characteristics of adult patients with PID and evaluate the relationship between laboratory values and comorbidities with disease and each other. This study included 55 adult PID patients receiving immunoglobulin replacement therapy. Demographic characteristics, laboratory parameters, treatment modalities, and clinical course of patients were recorded. The most common PID subtype was Common Variable Immunodeficiency. The most common initial complaints were related to the respiratory and digestive systems; 11 cancers were detected in 9 patients. None of the immunodeficiency patients with cancer were in the underweight group. IgA and platelet levels were higher in the group that developed cancer, and four patients have deceased. PIDs are multisystemic diseases. Early diagnosis and prompt treatment can lead to significant improvements in morbidity and mortality. Increased awareness and interdisciplinary cooperation are important.

Introduction

Primary immunodeficiencies (PID) are a group of disorders resulting from defects in the development and/or function of the immune system. They are characterized by recurrent and/or severe infections and are associated with an increased risk of allergic diseases, autoimmunity, and malignancies. While these infectious and noninfectious complications are often evident at the initial presentation, they may also emerge during the course of the disease.[1]

***Corresponding Author:** Yasemin Akgul Balaban, Division of Immunology and Allergic Diseases, Ankara Gulhane Training and Research Hospital, General Dr. Tevfik Sağlam cd. No:1 Etlik, Ankara, Turkey. *Email address*: yabalaban@gmail.com

https://doi.org/10.15586/aei.v54i3.1573

The clinical manifestations and disease severity can vary widely among individuals. Some patients may experience frequent infections, while others may present with milder symptoms or remain asymptomatic. This heterogeneity often complicates the diagnostic process and contributes to significant delays in diagnosis.[2] In addition to infections, patients may develop lymphoid hyperplasia, malignancies—particularly lymphomas—progressive interstitial lung disease, autoimmune manifestations, granulomatous inflammation, and hepatic or gastrointestinal involvement.[3,4] These immunodysregulatory features pose a significant clinical challenge, as their underlying pathogenesis remains poorly understood, and they typically do not respond to standard immunoglobulin replacement therapy (IgRT).[3,5]

In recent years, systemic inflammation markers have emerged as potential auxiliary tools for assessing disease activity and immunodysregulation in various chronic inflammatory conditions; however, their role in PID remains insufficiently explored. Likewise, the relationship between immunoglobulin patterns—such as elevated IgA levels—and clinical complications including malignancy has not been clearly defined in adult PID cohorts.

This study aims to address these knowledge gaps by evaluating systemic inflammation indices alongside immunoglobulin profiles and clinical outcomes in a well-characterized PID population.

With this approach, we aim not only to define our cohort but also to provide current data on systemic inflammation and immunoglobulin patterns as potential markers associated with disease complications, thereby contributing to the current understanding and follow-up strategies for PID patients.

Methods

This retrospective, cross-sectional, and descriptive study included a total of 55 patients diagnosed with PID and followed at the Adult Immunology and Allergy Clinic of Ankara Gulhane Training and Research Hospital between January 1, 2022 and January 1, 2023. PID diagnoses were made according to the clinical criteria of the European Society for Immunodeficiencies (ESID). Patients whose diagnoses met these standard criteria were included in the study. Secondary immunodeficiencies were systematically excluded through clinical and laboratory evaluation. Patients with any of the following were not included: uncontrolled diabetes mellitus, chronic renal failure, protein-losing states, malignancies or solid tumors, use of immunosuppressive agents (corticosteroids, biologics, chemotherapy) before PID diagnosis, HIV infection or other known causes of acquired immunodeficiency.

Among the patients, 47 were diagnosed with common variable immunodeficiency (CVID), 4 with Bruton's agammaglobulinemia, 1 with hyper IgM syndrome, 1 with CTLA-4 deficiency, and 2 with Good's syndrome; with these diagnoses supported by appropriate clinical, immunological, and—when applicable—genetic findings. Patients aged 18 years and older, of both sexes, whose complete clinical and laboratory data were available in the hospital's electronic medical records system, were included in the study. Patients under the age of 18 and those with inaccessible medical records were excluded.

Demographic characteristics, laboratory parameters, treatment approaches, and clinical course were recorded. Systemic inflammatory response markers—including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and pan-immune-inflammation value (PIV)—were calculated using blood samples obtained during clinically stable periods, defined as the absence of acute infection, exacerbation, or hospitalization within the preceding 4 weeks. Samples drawn during active infection or at the time of malignancy diagnosis were excluded to avoid confounding. Additionally, patients receiving systemic corticosteroids, cytotoxic agents, biologics, or short-term antibiotic therapy at the time of testing were not included in the inflammatory index analysis, as these treatments may influence hematologic parameters.

Serum immunoglobulin levels were measured using an immunoturbidimetric method on the Roche Cobas platform in the institutional clinical laboratory. Age-adjusted reference ranges are provided in Table 2.

The study was approved by the Ethics Committee of Ankara Gülhane Training and Research Hospital (Protocol Code: 2023/125).

Statistical Analysis

Data analysis of the study was performed using the IBM SPSS version 25.0 program. Descriptive statistics are presented as mean ± standard deviation (mean ± sd), median, 1st quartile, 3rd quartile, and minimum and maximum values for continuous variables. Categorical variables were expressed as numbers and percentages. The Shapiro-Wilk test was used to determine whether or not the data fitted the normal distribution, and Levene's test evaluated the homogeneity of variances in pairwise comparisons. Two independent group comparisons were made with the independent sample t test when the assumptions of normality and homogeneity of variances were met, with the independent sample t test when normality was met and the assumption of homogeneity of variances was not met, and with the Mann-Whitney U test when the assumption of normality was not met. Comparisons between categorical variables were evaluated using the Pearson chi-square test and Fisher's Exact Chi-square (for 2*2 table structure) and Exact chi-square (for table structures other than 2*2 table structure) tests when deemed necessary. Two dependent group comparisons were evaluated using the Wilcoxon signed-rank test because the assumption of normality was not met. The level of statistical significance was $P < 0.05$.

Results

Of the 55 patients included in the study, 63.6% (n = 35) were males and 36.4% (n = 20) were females. The median age of patients at the time of the study was 40 years, with the youngest being 20 and the oldest 70 years old. The median disease duration was 9.64 years, ranging from 0 to 34 years. The median age at symptom onset was 21 years

(range: 0–70 years), while the median age at diagnosis was 34 years (range: 1–72 years). The average diagnostic delay was 8 years (range: 1–37 years), and in 89.1% of patients (n = 49), this delay exceeded 5 years. A history of parental consanguinity was absent in 38 patients (69.1%), while 17 patients (30.9%) reported consanguineous parentage. Seven patients (12.7%) had a family history of immunodeficiency. Demographic characteristics of the patients are presented in Table 1, and laboratory findings are summarized in Table 2.

The most common initial complaints were related to the sinopulmonary system, observed in 81.9% of patients. This was followed by diarrhea in 21.8% and skin or mucosal findings in 9.1% of cases. Autoimmune diseases were the most frequently observed comorbidities, affecting 36.4% (n = 20) of the patients. These autoimmune conditions included autoimmune thyroiditis, autoimmune cytopenias (anemia, thrombocytopenia, neutropenia), rheumatoid arthritis, systemic lupus erythematosus, vitiligo, and psoriasis. When comparing the age at symptom onset between patients with and without autoimmune disease, those with autoimmune manifestations had a significantly higher median age at first complaint (28 vs 12 years; P = 0.046). Although the median age at diagnosis was also higher in patients with autoimmune disease, this difference did not reach statistical significance (41 vs 24 years; P = 0.122). Allergic diseases were identified in four patients, including drug allergy, allergic rhinitis, venom allergy, and food allergy.

Table 1 Demographic, clinical and radiologic characteristics of the patients.

Characteristics	Value
Sex (male/female, n [%])	35 (63.6%)/20 (36.4%)
Current age (years, median [min-max])	40 (20-70)
Age at first complaint (years, median [min-max])	21 (0-70)
Age at diagnosis (years, median [min-max])	34 (1-72)
Consanguinity, n (%)	17 (30.9%)
Family history of PID, n (%)	7 (12.7%)
BMI (kg/m^2, mean ± SD)	24.5 ± 3.8
Duration of illness (years, median [min-max])	9.64 (0-34)
Treatment (IVIG/SCIG)	46 (83.6%)/9 (16.4%)
Deaths, n (%)	4 (7.27%)
Blood type	
A, n (%)	20 (36.36%)
B, n (%)	11 (20%)
O, n (%)	18 (32.72%)
AB, n (%)	3 (5.45%)
RH$^+$, n (%)	47 (85.45%)
RH$^-$, n (%)	5 (9.09%)
Bronchiectasis, n (%)	19 (34.5%)
Organomegaly, n (%)	24 (43.6%)
Comorbidity,	
Autoimmune diseases, n (%)	20 (36.4%)
Cancer, n (%)	11 (20%)
Allergic diseases, n (%)	4 (7.3%)
Osteoporosis, n (%)	6 (10.9%)
Coronary artery diseases, n (%)	6 (10.9%)

Max: maximum; Min: minimum; PID: primary immunodeficiency; SD: standard deviation.

During the follow-up period, a total of 11 malignancies were identified in 9 patients (20%). Two patients were diagnosed with two different types of cancer. The malignancies that developed during the course of the disease included non-Hodgkin lymphoma (NHL), breast, gastric, and prostate cancers, and papillary thyroid carcinoma. Five patients had a history of malignancy before the diagnosis of immunodeficiency. These were primarily hematological cancers, including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and thymoma. Notably, four of the patients diagnosed with cancer also had coexisting autoimmune diseases. In addition, all patients who developed malignancy had Rh-positive blood types.

The median chronological age of patients who developed cancer was 51 years, which was significantly higher than that of patients without cancer in the cohort (P = 0.015). Additionally, the median age at the time of PID diagnosis was significantly higher in the cancer group compared to the noncancer group (48 vs 25 years; P = 0.049). Although the diagnostic delay was longer in the cancer group, the difference did not reach statistical significance. The mean body mass index (BMI) of the overall patient group was 24.5 ± 3.8 kg/m^2. According to BMI classification, 5 patients (9.1%) were underweight, 29 patients (52.7%) had normal weight, and 21 patients (38.2%) were overweight or obese. There was no statistically significant difference in BMI between patients who developed cancer and those who did not.

Inflammatory markers—including NLR, PLR, SII, and PIV—were higher in patients with autoimmune disease compared to those without. However, these differences were not statistically significant (Table 3). Similarly, although the same inflammatory markers (NLR, PLR, SII, and PIV) were elevated in patients who developed cancer compared to those who did not, the differences did not reach statistical significance. IgA levels tended to be higher in patients who developed cancer compared to those who did not (78 vs 5; P = 0.011), although the small sample size limits the generalizability of this finding. Platelet counts were also significantly higher in the cancer group (291 × 10^3 cells/uL vs 217 × 10^3 cells/uL; P = 0.048).

All patients were receiving IgRT, with 83.6% treated via intravenous immunoglobulin (IVIG) and 16.4% via subcutaneous immunoglobulin (SCIG). Among the patients receiving IVIG, 56.5% were males and 43.5% were females. All patients treated with SCIG were males. A statistically significant difference in gender distribution was observed between the two treatment groups (P = 0.019). Furthermore, the mean age of patients receiving SCIG treatment was significantly lower than that of patients receiving IVIG treatment (33.00 ± 7.57 vs 45.22 ± 16.15 years; P = 0.043).

Discussion

Primary immunodeficiencies are rare diseases that are often difficult to diagnose. Due to the variability in age

Table 2 The laboratory measurements of the patients.

Parameter	Value	Reference ranges
WBCs (×10³ cells/uL), median (Q1-Q3)	6.55 (4.80-8.00)	4.49-10.9
Hemoglobin (g/dL), mean ± SD	13.71 ± 2.03	11.9-14.6
Lymphocytes (×10³ cells/uL), median (Q1-Q3)	1.60 (1.20 - 2.00)	1.26-3.35
Platelets (×10³ cells/uL), median (Q1-Q3)	237.00 (165.00 - 298.00)	171-388
Monocytes (×10³ cells/uL), mean ± SD	0.53 ± 0.24	0.25-0.84
Neutrophiles (×10³ cells/uL), median (Q1-Q3)	4.20 (2.90 - 5.10)	2.1-8.89
Eosinophils (×10³ cells/uL), median (Q1-Q3)	0.1 (0.00 - 0.20)	0.01-0.4
MPV (fL), median (Q1-Q3)	9.3 (8.5 - 10.1)	7.5-11.2
Anti-TPO (IU/mL), median (Q1-Q3)	9.00 (4.05 - 19.15)	0-9
Uric acid (mg/dL), mean ± SD	5.01 ± 1.40	2.6-6
Vitamin D (ng/mL), median (Q1-Q3)	23.25 (14.00 - 36.63)	
Total protein (g/dL), mean ± SD	6.60 ± 0.75	5.7-8
Albumin (g/dL), mean ± SD	4.21 ± 0.48	3.5-5.2
Immunoglobulin levels		
IGG (mg/dL), mean ± SD	774.61 ± 414.08	700-1600
IGA (mg/dL), median (Q1-Q3)	7.50 (2.00-78.00)	70-400
IGM (mg/dL), median (Q1-Q3)	27.50 (10.00-51.30)	40-230
IGE (IU/mL), median (Q1-Q3)	1.57 (1.00-18.00)	0-87
IGG subgroups		
IGG1 (g/L), mean ± SD	5.51 ± 3.18	4.05-10.11
IGG2 (g/L), median (Q1-Q3)	2.04 (1.08-3.34)	1.69-7.86
IGG3 (g/L), median (Q1-Q3)	0.20 (0.17-0.30)	0.11-0.85
IGG4 (g/L), median (Q1-Q3)	0.10 (0.03-0.18)	0.03-2.01
Lymphocyte subgroups		
CD56 (%), median (Q1-Q3)	11.40 (6.60-16.90)	6-29
CD4 (%), mean ± SD	39.81 ± 12.76	34-63.8
CD8 (%), mean ± SD	42.45 ± 14.48	19-48
CD19 (%), median (Q1-Q3)	5.10 (1.30-9.83)	7-23
CD16 (%), median (Q1-Q3)	8.70 (4.50-14.40)	6-29
CD3 (%), median (Q1-Q3)	81.77 (76.00 -87.40)	62.8-85

Table 3 Inflammatory marker status in autoimmunity and cancer.

	With autoimmunity	Without autoimmunity	P	With cancer	Without cancer	P
NLR median (Q1-Q3)	2.67 (1.91-4.60)	2.40 (1.60-3.14)	0.267	2.35 (1.65-3.62)	2.47 (1.69-3.259)	0.963
PLR median (Q1-Q3)	133.04 (96.26-216.32)	130.67 (93.33-160.00)	0.579	186.47 (146.47-234.62)	120.00 (93.33-160.71)	0.052
SII median (Q1-Q3)	659.31 (304.69-1043.22)	561.81 (384.00-768.87)	0.400	708.59 (401.12-1102.69)	565.95 (309.38-812.50)	0.242
PIV median (Q1-Q3)	353.55 (125.51-674.43)	300.97 (128.08-407.58)	0.316	354.29 (126.98-744.87)	306.51 (127.26-494.00)	0.433

of onset and clinical presentation, diagnostic delays are common.[1] In our patient cohort, the median age at diagnosis and the diagnostic delay were 34 and 8 years, respectively. Muşabak et al. reported a longer diagnostic delay of 19.9 ± 9.3 years compared to our findings.[6] Similarly, Carvalho et al. found the mean age at onset of initial symptoms and at diagnosis to be 12 and 22 years, respectively, which are lower than the corresponding ages in our study.[7] Ardeniz et al. reported a mean age at diagnosis of 33 years in women and 28 years in men, with diagnostic delays of 15 years in women and 8 years in men.[8] We believe that the differences observed in age at diagnosis and diagnostic delay among these studies may be related to variations in PID awareness across different time periods and geographic regions. Increasing awareness among physicians has likely contributed to a higher recognition of PID than previously assumed.

CVID is the most common symptomatic form of PID in the adult population.[1] Consistent with the literature, CVID was the predominant PID subtype in our patient cohort. Splenomegaly and hepatomegaly were observed either separately or concurrently in some patients. Wehr et al. reported a splenomegaly prevalence of 40.5%,[9] which is comparable to our rate of 43.6%. Other studies reported

splenomegaly frequencies of 38% (Oksenhendler et al.), 30.4% (Patuzzo et al.), and 30% (Chapel et al.).[10-12] In contrast, Muşabak et al. found a higher splenomegaly rate of 61.3% and hepatomegaly rate of 22.6%. We also examined potential associations between organomegaly and lymphocyte subpopulations. Patients with organomegaly exhibited lower CD56, CD16, and CD4 counts and higher CD8, CD19, and CD3 counts compared to those without organomegaly; however, these differences did not reach statistical significance.

In a study conducted by the European Chest CT Group involving 282 patients from nine countries, bronchiectasis was reported as the most common radiologic abnormality, observed in 61% of patients with primary antibody deficiency.[13] The frequency of bronchiectasis in our patient cohort was 34.5%, which is similar to the rate reported by Oksenhendler et al. (37%), but lower than the frequencies reported by Muşabak et al. and Thickett et al. (61.2 and 68.1%, respectively).[6,14] We hypothesize that the lower frequency in our cohort may be attributed to a shorter diagnostic delay. Regarding immunological parameters, CD8, CD19, CD3, CD56, CD16, and CD4 counts were lower in patients with bronchiectasis compared to those without; however, these differences did not reach statistical significance.

Primary Immunodeficiency is associated not only with recurrent and severe infections but also with an increased risk of allergic diseases, autoimmune conditions, and malignancies. Among the cancers most frequently observed in PID patients are lymphomas—particularly NHL—as well as various solid organ tumors.[4] A total of 11 cancer cases were identified in our patient cohort. Five of these patients had a history of cancer before the diagnosis of immunodeficiency, while six developed cancer during the follow-up period after being diagnosed with PID. Among these six patients, cancer was diagnosed after 8 years in two cases, after 11 years in three cases, and after 18 years in one case. The malignancies observed included hematologic cancers such as ALL, CLL, and NHL, along with solid tumors such as thymoma, papillary thyroid carcinoma, gastric cancer, and prostate cancer—findings consistent with those reported in the literature.[6,15,16] Although the association between PID and an increased risk of cancer is well established, the underlying pathophysiological mechanisms remain poorly understood.[15] Like two sides of the same coin, patients may initially present with either immunodeficiency or malignancy—or both—making it essential to adopt a standardized, interdisciplinary approach to diagnosis and management. In particular, when evaluating lymphoproliferative malignancies, clinicians should consider the possibility of an underlying PID. It is also important to follow patients closely in the short and long term with regard to cancer development.

Although weight loss is generally considered an important indicator of malignancy, this finding was not consistent in our study.[17] Notably, none of the immunodeficient patients with cancer in our cohort were classified in the underweight group. This may be related to the fact that these patients were receiving IgRT at the time. IgRT may help mask weight loss by reducing systemic inflammation or by stabilizing the patient's overall health status. However, the absence of weight loss—particularly in PID patients undergoing IgRT—should not be interpreted as an absence of malignancy. Therefore, we recommend a more cautious and systematic screening approach for malignancy in this patient group.

For many years, it was believed that immunoglobulins (Ig) were produced exclusively by B cells. However, accumulating evidence now suggests that cancer cells themselves can produce high levels of immunoglobulins.[18] Notably, cancer-derived immunoglobulins have been identified in a variety of epithelial malignancies—including breast, colon, prostate, thyroid, gastric, pancreatic, and liver cancers—as well as in soft tissue tumors such as fibrosarcoma, and hematologic malignancies like acute myeloid leukemia (AML).[18] In our cohort, the malignancies observed were predominantly epithelial and hematologic in nature. The elevated IgA levels identified in patients who developed malignancy may therefore represent an associated immunologic finding in this context. Given that immunoglobulin replacement therapy (IgRT) preparations generally contain only minimal amounts of IgA due to the risk of anaphylaxis in IgA-deficient individuals,[19] IgRT is unlikely to be a major contributor to the observed IgA elevation. Nevertheless, the retrospective design and limited sample size of the present study preclude definitive conclusions regarding the source of IgA elevation. Elevated IgA levels may thus serve as a potential marker associated with malignancy in patients with primary immunodeficiency; however, no causal inference can be drawn. Further well-designed, prospective studies are required to validate this association and clarify its clinical significance.

Several studies investigating the potential determinants of hematologic malignancy risk in patients with CVID have reported conflicting findings. While some studies suggest a link between elevated IgM levels and malignancy, others have proposed that low IgM levels may be associated with increased cancer risk. In contrast to these findings, our study demonstrated that CVID patients who developed cancer exhibited statistically significant elevations in IgA levels, rather than IgM.[3,12,20,21]

The association between blood type and disease has been a topic of research for many years. While ABO blood groups have been extensively studied in relation to cancer, no clear link has been established with the Rh factor. Although establishing a direct causal relationship remains difficult, it is noteworthy that in our study, all immunodeficient patients who developed cancer had Rh-positive blood types.[22-24]

The standard treatment for patients with PID is IgRT, which can be administered either intravenously (IVIG) or subcutaneously (SCIG). Given that IgRT is a lifelong and costly intervention, the choice of administration route should be made with careful consideration of both clinical and patient-related factors. Numerous studies have demonstrated that IgRT significantly improves patient outcomes, including both subjective enhancements in quality of life and objective reductions in infection frequency, infection severity, and hospitalization rates.[19,25] In our cohort, all patients were receiving IgRT. Treatment efficacy and potential adverse effects were routinely evaluated during outpatient visits, and both IVIG and SCIG options were discussed with each patient. Treatment decisions were made collaboratively. Nine out of 55 patients opted for SCIG.

The lower average age observed in the SCIG group may reflect a preference among younger individuals, possibly due to their more active social and professional lives. SCIG allows patients to avoid frequent hospital visits—typically required every 3–4 weeks for IVIG—thereby reducing disruption to daily routines such as school, work, and social activities. Interestingly, none of the female patients in our study chose SCIG. This may be attributed to potential cosmetic concerns related to subcutaneous administration sites, which could affect treatment preferences.

During the follow-up period, four patients died. The causes of death included three cases of malignancy—two hematologic and one gastric—and one case of renal failure secondary to amyloidosis. Although secondary amyloidosis is a rare complication in patients with immunodeficiency, it carries a high risk of mortality due to its potential for multiorgan involvement.[26] Therefore, clinicians should remain vigilant for this serious complication during long-term follow-up.

Our study is limited by its retrospective and single-center design, as well as a relatively small sample size and short follow-up period. To more accurately identify factors influencing the prognosis of PIDs, prospective studies with larger, multicenter cohorts and longer follow-up durations are needed. These studies would enhance statistical power and provide more robust evidence. Although we observed higher inflammatory markers in PID patients with cancer and autoimmune comorbidities compared to those without, the lack of statistically significant findings may be due to our limited sample size and follow-up time. Therefore, future well-designed, long-term, multicenter prospective studies are crucial to better understand these associations and improve patient outcomes.

Conclusion

In our study, the most common PID subgroup was CVID, with sinopulmonary complaints being the most frequent initial symptoms and autoimmunity the most common comorbidity. In particular, we find it noteworthy that IgA levels were elevated in patients who developed cancer and that one patient died due to amyloidosis complications.

Primary Immunodeficiencies present with diverse clinical manifestations, including severe or recurrent infections, allergic diseases, malignancies, and autoimmune disorders. As multisystem diseases, PIDs require management by a multidisciplinary team led by an immunologist. Early diagnosis and timely treatment are crucial for reducing morbidity and mortality, highlighting the importance of increased awareness and interdisciplinary collaboration.

All authors have given their final approval of the version and accept responsibility for all aspects of the work.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Author Contributions

All authors contributed equally to this article.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

Funding

None.

References

1. Ho HE, Cunningham-Rundles C. Seeking relevant biomarkers in common variable immunodeficiency. Front Immunol. 2022;13:857050. https://doi.org/10.3389/fimmu.2022.857050
2. Mertowska P, Smolak K, Mertowski S, Grywalska E. Unraveling the role of toll-like receptors in the immunopathogenesis of selected primary and secondary immunodeficiencies. Cells. 2023;12(16):2055. https://doi.org/10.3390/cells12162055
3. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119(7):1650–7. https://doi.org/10.1182/blood-2011-09-377945
4. Ho HE, Cunningham-Rundles C. Non-infectious complications of common variable immunodeficiency: Updated clinical spectrum, sequelae, and insights to pathogenesis. Front Immunol. 2020;11:149. https://doi.org/10.3389/fimmu.2020.00149
5. Fischer A, Provot J, Jais JP, Alcais A, Mahlaoui N; members of the CEREDIH French PID study group. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immunol. 2017;140(5):1388–1393.e8.
6. Muşabak UH, Erdoğan T. Clinical features and immunoglobulin replacement therapy outcomes of adults with common variable immunodeficiency: A single centre experience. Turk J Med Sci. 2021;51(5):2427–36. https://doi.org/10.3906/sag-2010-82
7. Carvalho KI, Melo KM, Bruno FR, Snyder-Cappione JE, Nixon DF, Costa-Carvalho BT, et al. Skewed distribution of circulating activated natural killer T (NKT) cells in patients with common variable immunodeficiency disorders (CVID). PLoS One. 2010;5(9):e12652. https://doi.org/10.1371/journal.pone.0012652
8. Ardeniz O, Başoğlu OK, Günşar F, Unsel M, Bayraktaroğlu S, Mete N, et al. Clinical and immunological analysis of 23 adult patients with common variable immunodeficiency. J Investig Allergol Clin Immunol. 2010;20(3):222–36.
9. Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood. 2008;111(1):77–85. https://doi.org/10.1182/blood-2007-06-091744
10. Oksenhendler E, Gérard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, et al. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis. 2008;46(10):1547–54. https://doi.org/10.1086/587669
11. Patuzzo G, Mazzi F, Vella A, Ortolani R, Barbieri A, Tinazzi E, et al. Immunophenotypic analysis of B lymphocytes in patients with common variable immunodeficiency:

identification of CD23 as a useful marker in the definition of the disease. ISRN Immunology. 2013;201:512527. https://doi.org/10.1155/2013/512527
12. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: Division into distinct clinical phenotypes. Blood. 2008;112(2):277–86. https://doi.org/10.1182/blood-2007-11-124545
13. Schütz K, Alecsandru D, Grimbacher B, Haddock J, Bruining A, Driessen G, et al. Imaging of bronchial pathology in antibody deficiency: Data from the European Chest CT Group. J Clin Immunol. 2019;39(1):45–54. https://doi.org/10.1007/s10875-018-0577-9
14. Thickett KM, Kumararatne DS, Banerjee AK, Dudley R, Stableforth DE. Common variable immune deficiency: Respiratory manifestations, pulmonary function and high-resolution CT scan findings. QJM. 2002;95(10):655–62. https://doi.org/10.1093/qjmed/95.10.655
15. Tak Manesh A, Azizi G, Heydari A, Kiaee F, Shaghaghi M, Hossein-Khannazer N, et al. Epidemiology and pathophysiology of malignancy in common variable immunodeficiency? Allergol Immunopathol (Madr). 2017;45(6):602–15. https://doi.org/10.1016/j.aller.2017.01.006
16. Ballow M, Sánchez-Ramón S, Walter JE. Secondary immune deficiency and primary immune deficiency crossovers: Hematological malignancies and autoimmune diseases. Front Immunol. 2022;13:928062. https://doi.org/10.3389/fimmu.2022.928062
17. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers. 2018;4:17105. https://doi.org/10.1038/nrdp.2017.105
18. Cui M, Huang J, Zhang S, Liu Q, Liao Q, Qiu X. Immunoglobulin expression in cancer cells and its critical roles in tumorigenesis. Front Immunol. 2021;12:613530. https://doi.org/10.3389/fimmu.2021.613530
19. Perez EE, Orange JS, Bonilla F, Chinen J, Chinn IK, Dorsey M, et al. Update on the use of immunoglobulin in human disease: A review of evidence. J Allergy Clin Immunol. 2017;139(3S):S1-S46. https://doi.org/10.1016/j.jaci.2016.09.023
20. Kiaee F, Azizi G, Rafiemanesh H, Zainaldain H, Sadaat Rizvi F, Alizadeh M, et al. Malignancy in common variable immunodeficiency: A systematic review and meta-analysis. Expert Rev Clin Immunol. 2019;15(10):1105–13. https://doi.org/10.1080/1744666X.2019.1658523
21. Wehr C, Houet L, Unger S, Kindle G, Goldacker S, Grimbacher B, et al. Altered spectrum of lymphoid neoplasms in a single-center cohort of common variable immunodeficiency with immune dysregulation. J Clin Immunol. 2021;41(6):1250–65. https://doi.org/10.1007/s10875-021-01016-4
22. Yu H, Xu N, Li ZK, Xia H, Ren HT, Li N, et al. Association of ABO blood groups and risk of gastric cancer. Scand J Surg. 2020;109(4):309–13. https://doi.org/10.1177/1457496919863886
23. Abegaz SB. Human ABO blood groups and their associations with different diseases. Biomed Res Int. 2021;2021:6629060.0020. https://doi.org/10.1155/2021/6629060
24. Yang H, Yan J. A systematic review of prognosis of ABO blood group and rhesus factor on outcomes in patients with bladder cancer. Medicine (Baltimore). 2022;101(39):e30893. https://doi.org/10.1097/MD.0000000000030893
25. Quinti I, Soresina A, Guerra A, Rondelli R, Spadaro G, Agostini C, et al. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: Results from a multicenter prospective cohort study. J Clin Immunol. 2011;31(3):315–22. https://doi.org/10.1007/s10875-011-9511-0
26. Esenboga S, Çagdas Ayvaz D, Saglam Ayhan A, Peynircioglu B, Sanal O, Tezcan I. CVID associated with systemic amyloidosis. Case Reports Immunol. 2015;2015:879179. https://doi.org/10.1155/2015/879179