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Clinical and immunological heterogeneity in common variable immunodeficiency: a cluster analysis of a single-center cohort

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Abstract

Introduction: *Common variable immunodeficiency (CVID) presents with diverse clinical and immunological manifestations. This study aimed to investigate the relationships between clinical phenotypes and immunological profiles in an adult CVID cohort.*

Material and methods: *We retrospectively evaluated demographic and clinical features, infectious/non-infectious complications, immunological parameters, and flow cytometric findings in 32 adult patients (aged ≥ 18 years; 14 female, 18 male) diagnosed with CVID.*

Results: *Based on clinical phenotypes and organ system involvement, three clusters were identified: Cluster 1 (n = 10, 31.2%) was characterized by dominant infectious phenotype; Cluster 2 (n = 8, 25.0%) featured infectious manifestations but lacked lymphoproliferation; allergic conditions were relatively more common; and Cluster 3 (n = 14, 43.8%) was distinguished by dominant autoimmune features and lymphoproliferation. The most frequently observed cluster in our patient cohort was Cluster 3. The most significant predictors in the clustering analysis were lymphoproliferation, autoimmunity, and infection. The percentage of $CD4^+CD45RO^+$ cells was significantly higher in patients without infections, whereas the percentage of $CD8^+CD45RO^+$ cells was higher in those with infections ($p = 0.007$ and 0.003, respectively). Among patients with autoimmunity, $CD8^+CD45RO^+$ percentages were lower and $CD21^{low}CD38^{low}$ B cell populations were higher compared to those without autoimmunity ($p = 0.005$ and $p = 0.047$, respectively).*

Conclusions: *This study highlights infection, autoimmunity, and lymphoproliferation as prominent phenotypic features in CVID and reveals distinct immune cell profiles among these phenotypes. These findings may provide valuable guidance for improving diagnostic processes and patient management in CVID.*

Key words: *common variable immunodeficiency, infection, autoimmunity, immunophenotyping, lymphoproliferation, flow cytometry.*

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Introduction

Common variable immunodeficiency (CVID) is one of the most frequently encountered primary immunodeficiencies, with an estimated prevalence ranging between 1 : 25,000 and 1 : 50,000 in the general population. The European Society for Immunodeficiencies (ESID) defines CVID by a marked reduction in serum levels of immunoglobulin (Ig) G, IgA, and/or IgM, poor antibody responses to vaccines, and the exclusion of other causes of hypogammaglobulinemia, including malignancies, infections, and drug-induced immunosuppression [1, 2]. Despite the existence of diagnostic criteria, CVID is a highly heterogeneous condition, both clinically and immunologically.

Approximately 80% of CVID patients experience recurrent infections, particularly affecting the respiratory tract [3]. However, infectious manifestations may coexist with, or even be preceded by, non-infectious complications, such as autoimmunity, chronic inflammation, lymphoproliferative disorders, and malignancies. Notably, autoimmune phenomena, including cytopenias, thyroiditis, psoriasis, and arthritis, are observed in up to 30% of pa-

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tients and may represent the initial clinical presentation in a subset of individuals [4, 5]. Additional organ involvement, such as pulmonary granulomatous disease, enteropathy, and dermatologic manifestations, further contributes to the disease's complexity [4, 6].

While several monogenic defects associated with CVID have been identified, the underlying genetic cause remains unknown in the majority of patients [7, 8]. Most cases are sporadic, and diagnosis often occurs in adolescence or early adulthood, with a peak incidence between ages 25 and 45 [9]. The immunopathology of CVID commonly includes defects in B cell maturation and function, particularly involving reduced numbers of class-switched memory B cells and expansion of $CD21^{low}$ B cells. These abnormalities have been linked to increased susceptibility to autoimmune cytopenias, granulomatous inflammation, and lymphoid hyperplasia [10].

Phenotypic heterogeneity in CVID has prompted numerous efforts to correlate clinical subgroups with specific immunological signatures. Studies have demonstrated that patients with autoimmune or inflammatory features tend to show lower switched memory B cells, increased $CD21^{low}$ B cells, and alterations in T cell subsets, such as decreased naive $CD4^+$ T cells [11, 12]. These immunophenotypic features have potential utility in predicting disease course and guiding individualized management strategies. Moreover, patients with non-infectious complications often demonstrate worse long-term outcomes compared to those with predominantly infectious phenotypes [4, 6].

Importantly, significant variation exists across different countries and clinical centers in terms of phenotype prevalence and immunological profiles. Therefore, the integration of clinical and immunophenotypic data through systematic approaches, such as cluster analysis, may offer valuable insights into underlying disease mechanisms and help identify high-risk subgroups.

In this study, we aimed to explore the clinical and immunological heterogeneity of CVID in a single-center cohort using a data-driven cluster analysis approach. By delineating associations between clinical phenotypes and immunological parameters, we seek to contribute to a more nuanced understanding of CVID subtypes and to provide evidence that may inform future risk stratification and personalized care strategies.

Material and methods

Study design and participants

This retrospective cohort study included adult patients (aged ≥ 18 years) who were diagnosed with CVID and followed at our immunology outpatient clinic between February 2019 and December 2024. All patients fulfilled the diagnostic criteria for CVID as revised by the ESID. Patients with hypogammaglobulinemia secondary to malignancy, infections, protein-losing enteropathy, or immunosuppressive medications were excluded.

The study protocol was approved by the Scientific Research and Ethics Committee of Ankara Bilkent City Hospital (Approval date: September 4, 2024; TABED no. 2-24-440). The study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design, the requirement for informed consent was waived by the ethics committee.

Data collection

Demographic, clinical, and laboratory data were extracted from electronic health records and archived patient files. Collected variables included age, sex, medical history, serum immunoglobulin levels, complete blood counts, lymphocyte subset analyses by flow cytometry, pulmonary function tests, radiological assessments (ultrasonography, computed tomography), endoscopic evaluations (gastroscopy, colonoscopy), and pathology results.

Clinical phenotyping and grouping

Patients were categorized into subgroups based on the presence of specific clinical features:

Infectious phenotype: recurrent infections. Lymphoproliferative phenotype: lymphadenopathy, hepatomegaly, splenomegaly, granulomatous-lymphocytic interstitial lung disease (GLILD). Autoimmune phenotype: autoimmune hemolytic anemia, immune thrombocytopenia, Evans syndrome, autoimmune neutropenia, autoimmune hepatitis, thyroiditis, type 1 diabetes mellitus, systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, and other autoimmune or rheumatic disorders. Allergic phenotype: asthma, allergic rhinitis, drug allergy, atopic dermatitis, anaphylaxis. Autoinflammatory phenotype: diagnosed systemic autoinflammatory syndromes. Malignancy: CVID-related or unrelated neoplasms.

In addition, patients were evaluated for evidence of organ involvement unrelated to the primary CVID phenotype, including respiratory, gastrointestinal, and dermatological systems.

Laboratory measurements

At the time of initial presentation to the hospital, all patients underwent laboratory testing, including routine complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement components C3 and C4, immunoglobulins, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, thyroid-stimulating hormone (TSH), total protein, albumin, complete urinalysis, hemogram, and antinuclear antibody (ANA) testing. All laboratory data were obtained from the Central Laboratory of Ankara Bilkent City Hospital.

Serum immunoglobulin measurements

Serum IgG, IgA, IgM, and IgG subclasses (IgG1-4) levels at diagnosis were measured by nephelometry using the Siemens BNII System (Erlangen, Germany).

Flow cytometric immunophenotyping

Peripheral lymphocyte subsets – $CD4^+$ T cells, $CD8^+$ T cells, $CD19^+$ B cells, and $CD3^-/CD16^+CD56^+$ natural killer (NK) cells – were analyzed using the Kaluza software on the Beckman Coulter Navios EX flow cytometry system (Becton Dickinson, USA). For extracellular staining of surface markers, fluorescence-conjugated monoclonal antibodies were used as follows: for lymphocyte subsets – CD45 KO, CD4 ECD, CD8 PC7, CD3 FITC, $CD16^+$CD56 PE, CD19 PC5.5, CD20 Alexa 700, and HLA-DR PB; for B cell subsets – IgD PE, CD19 ECD, CD27 PC5.5, CD38 Alexa 750, CD21 PB, and CD45 KO; for T cell subsets – CD45RO FITC, CD31 PE, CD4 ECD, CD8 PC7, CD45RA APC, CD3 Alexa 750, and CD45 KO. Surface expression of the analyzed cells was determined as percentages.

Imaging and endoscopic assessment

The most recent thoracic high-resolution computed tomography (HRCT), abdominal ultrasonography, lymph node ultrasonography, and, when applicable, abdominal CT, bronchoscopy, endoscopy, and colonoscopy findings were reviewed to evaluate systemic organ involvement.

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive data were presented as frequencies, percentages, means with standard deviations, or medians with interquartile ranges, as appropriate. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of continuous variables. Categorical variables were compared using the chi-square test. Continuous variables were analyzed using either parametric (*t*-test, ANOVA) or non-parametric tests (Mann-Whitney *U*, Kruskal-Wallis), based on distribution characteristics. Correlations between variables were assessed using Pearson or Spearman correlation coefficients. Patients were further stratified by phenotype using cluster analysis to identify natural groupings based on clinical and immunological profiles. A two-step cluster analysis was performed in SPSS (version 25.0) to identify natural groupings among patients based on clinical and immunological variables. This approach accommodates both categorical and continuous data, and the optimal number of clusters was determined automatically using Schwarz's Bayesian Criterion (BIC). A p-value of < 0.05 was considered statistically significant.

Results

A total of 32 patients diagnosed with common variable immunodeficiency (CVID) were retrospectively evaluated, comprising 14 females (43.8%) and 18 males (56.3%). The mean age at the time of analysis was 37.03 ±13.08 years. The median age at diagnosis was 23 years (range: 2-64), with a median diagnostic delay of 3 years (range: 0-26) (Table 1). Parental consanguinity was present in 11 patients (34.4%), and no patients reported a family history of immunodeficiency.

The most frequently observed clinical phenotype was recurrent infections, present in 25 patients (78.1%). This was followed by lymphoproliferative phenotype in 24 (75.0%) and autoimmune phenotype in 17 (53.1%) patients. Allergic phenotypes were identified in 11 patients (34.4%) (Table 2). Within the lymphoproliferative phenotype, splenomegaly was the most common (53.1%), followed by lymphadenopathy (46.9%) and hepatomegaly (46.9%). The most frequent autoimmune phenotypes included autoimmune thyroiditis (18.8%), immune thrombocytopenia (15.6%), autoimmune hemolytic anemia (6.3%), and Evans syndrome (6.3%).

The respiratory system was the most frequently affected organ system, with involvement in 20 patients (62.5%). Bronchiectasis was the predominant respiratory finding (n = 12, 37.5%), followed by interstitial lung disease or bronchiolitis obliterans in 9 (28.1%) and granulomatous-lymphocytic interstitial lung disease (GLILD) in 2 (6.3%) patients. Gastrointestinal involvement was present in 7 patients (21.9%) and cutaneous involvement in 8 (25.0%).

When patients were stratified by age at diagnosis (< 20 vs. ≥ 20 years), allergic diseases were significantly more frequent in the ≥ 20-year group (p = 0.023), while no differences were observed for other phenotypes or organ system involvement (all $p > 0.05$).

Table 1. Demographic and clinical characteristics of patients (n = 32)

Parameter	Value
Sex, *n* (%)	
Female	14 (43.8)
Male	18 (56.3)
Age (years), mean ±SD	37.03 ±13.08
Age at diagnosis (years), median (min-max)	23 (2-64)
Age at symptom onset (years), median (min-max)	19 (4-58)
Diagnostic delay (years), mean ±SD	3 (0-26)
Parental consanguinity, *n* (%)	11 (34.4)
Family history of immunodeficiency, *n* (%)	0 (0)

Table 2. Phenotypic features and non-infectious organ/system involvement of patients

Phenotype	**Clinical involvement**	***n* (%)**
Infections	25 (78.1)	
	Recurrent upper respiratory tract infections (viral/bacterial)	16 (50.0)
	Pneumonia	13 (40.6)
	Otitis	5 (15.6)
	Bacterial sinusitis	2 (6.3)
	Meningitis	2 (6.3)
	Gastroenteritis	1 (3.1)
	Deep abscess	1 (3.1)
Lymphoproliferation	24 (75)	
	Splenomegaly	17 (53.1)
	Lymphadenopathy	15 (46.9)
	Hepatomegaly	15 (46.9)
	GLILD (granulomatous-lymphocytic interstitial lung disease)	2 (6.3)
Autoimmunity	17 (53.1)	
	Autoimmune thyroiditis	6 (18.8)
	Autoimmune thrombocytopenia	5 (15.6)
	Autoimmune hemolytic anemia	2 (6.3)
	Evans syndrome	2 (6.3)
	Celiac disease	2 (6.3)
	Vitiligo	2 (6.3)
	Rheumatoid arthritis / Systemic lupus erythematosus / Sjögren's syndrome	2 (6.3)
	Immune neutropenia	1 (3.1)
	Autoimmune hepatitis	1 (3.1)
	Type 1 diabetes mellitus	1 (3.1)
Autoinflammation	1 (3.1)	
Allergy	11 (34.4)	
	Asthma	6 (18.8)
	Atopic dermatitis	3 (9.4)
	Drug allergy	2 (6.3)
	Allergic rhinitis	1 (3.1)
Malignancy	2 (6.3)	
	Lymphoma	2 (6.3)
Organ/System involvement	**Involvement type**	***n* (%)**
Respiratory	20 (62.5)	
	Bronchiectasis	12 (37.5)
	Interstitial lung disease / Bronchiolitis obliterans	9 (28.1)
	GLILD	2 (6.3)
Gastrointestinal	7 (21.9)	
	Nodular lymphoid hyperplasia	3 (9.4)
	Celiac disease	2 (6.3)
	Inflammatory bowel disease	1 (3.1)
	Chronic hepatitis of unknown etiology	1 (3.1)
Skin	8 (25.0)	
	Other types of dermatitis	4 (12.5)
	Atopic dermatitis	3 (9.4)
	Vitiligo	1 (3.1)

Input predictor importance 1.0 0.8 0.6 0.4 0.2 0

Input	Cluster 1	Cluster 2	Cluster 3
Description	Dominated by the infectious phenotype	Infectious manifestations, lacked lymphoproliferation; allergic conditions were relatively common	Characterized by prominent autoimmunity and lymphoproliferation
Size, % (*n*)	31.2 (10)	25.0 (8)	43.8 (14)
Infection (%)	Present (100.0)	Present (87.5)	Present (57.1)
Lymphoproliferation (%)	Absent (70.0)	Absent (100.0)	Present (100.0)
Autoimmunity (%)	Absent (100.0)	Absent (62.5)	Present (100.0)
Respiratory involvement (%)	Present (70.0)	Present (62.5)	Present (71.4)
Allergy (%)	Present (70.0)	Absent (50.0)	Absent (71.4)
GI involvement (%)	Present (60.0)	Absent (100.0)	Present (92.9)
Malignancy (%)	Absent (90.0)	Absent (100.0)	Absent (92.9)
Autoinflammation (%)	Absent (90.0)	Absent (100.0)	Absent (100.0)

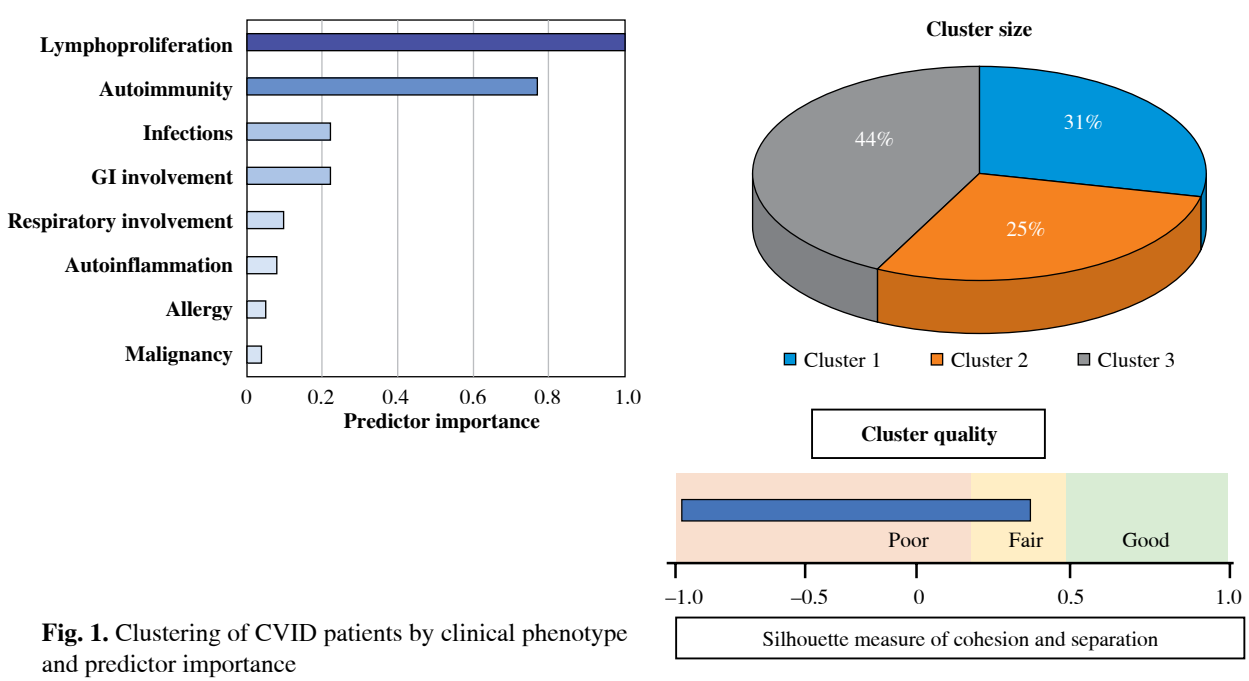

Fig. 1. Clustering of CVID patients by clinical phenotype and predictor importance

Cluster analysis

A cluster analysis was performed to explore phenotypic and organ-specific heterogeneity. Three distinct clusters were identified (Fig. 1):

- Cluster 1 (n = 10, 31.2%): Dominated by the infectious phenotype;
- Cluster 2 (n = 8, 25.0%): Featured infectious manifestations but lacked lymphoproliferation; allergic conditions were relatively more common;
- Cluster 3 (n = 14, 43.8%): Characterized by prominent autoimmunity and lymphoproliferative features.

Cluster 3 was the most prevalent pattern in our cohort. Infection, autoimmunity, and lymphoproliferation emerged as the strongest predictive features for cluster assignment (Fig. 1).

Immunological profile and laboratory comparisons

Laboratory parameters including immunoglobulin levels, complement components, and peripheral blood leukocyte and lymphocyte subsets were analyzed in relation to clinical phenotypes (Table 3). Patients with infections had significantly higher leukocyte (p = 0.010), neutrophil (p = 0.024), lymphocyte (p = 0.034), and monocyte (p = 0.006) counts. Complement levels (C3 and C4) were also elevated in this group (p = 0.001 and p = 0.039, respectively) (Table 4).

Flow cytometric analysis showed that $CD4^+CD45RO^+$ memory T cell percentages were significantly higher in patients without infections (p = 0.007), whereas $CD8^+$ $CD45RO^+$ T cell percentages were elevated in those with infections (p = 0.003). In patients with autoimmunity, $CD8^+CD45RO^+$ T cells were lower compared to those without autoimmunity (p = 0.005), while activated B cells ($CD21^{low}CD38^{low}$) were significantly elevated (p = 0.047). No significant immunological differences were observed between patients with and without lymphoproliferative involvement (all $p > 0.05$) (Table 5).

$CD3^-CD16^+CD56^+$ NK cell percentages were significantly higher in the ≥ 20-year group (10.73 ±10.68 vs. 4.75 ±3.61; p = 0.043) (Table 5). No significant differences in clinical phenotypes, organ involvement, or laboratory parameters were found across diagnostic delay categories (no delay, 1-5 years, > 5 years).

Other clinical outcomes

Two patients (6.3%) died during follow-up due to sepsis secondary to pulmonary infections; both had underlying bronchiectasis. Malignancy was detected in two patients (6.3%), both cases were Hodgkin lymphoma. Additionally, one patient (3.1%) had a co-diagnosis of familial Mediterranean fever (FMF), and three patients (9.4%) had evidence of granulomatous disease, including two with GLILD and one with Crohn's disease.

Discussion

In this single-center cohort study, we comprehensively investigated the clinical and immunological heterogeneity of CVID using a cluster analysis approach. Our findings confirm that CVID is a highly heterogeneous primary immunodeficiency characterized by marked variability in clinical presentation, immunological profiles, and disease course. Such heterogeneity has been consistently demonstrated across previously reported cohorts with 6.5 to 20-year follow-ups [13-15].

Recurrent infections, particularly involving the respiratory tract, were the most common clinical phenotype in our cohort, observed in over three-quarters of patients. Lymphoproliferative manifestations and autoimmune diseases were also highly prevalent, occurring in 75.0% and 53.1% of patients, respectively. These findings are in line with earlier studies highlighting immune dysregulation, lymphoid hyperplasia, and susceptibility to autoimmunity as hallmark features of CVID [6, 16, 17].

Despite the consistent observation of recurrent infections as a defining feature, numerous studies have demonstrated that non-infectious complications, including autoimmunity, lymphoproliferation, granulomatous disease, and malignancies, significantly contribute to morbidity and mortality in CVID [4, 6, 18]. Our cluster analysis revealed three distinct patient groups based on combinations of infection, autoimmunity, lymphoproliferation, and allergic phenotypes. Notably, the largest cluster (43.8% of patients) was characterized by prominent autoimmunity and lymphoproliferation, with all individuals in this group exhibiting autoimmune disease. Previous studies have emphasized that such patients may have a more complex clinical trajectory, higher risk of granulomatous lung disease, malignancy, and worse long-term outcomes [4, 6, 19].

Our study also confirmed that lymphoproliferation, autoimmunity, and infection history were the strongest predictors of cluster assignment. These observations align with a recent meta-analysis of 8,521 CVID patients, which identified recurrent respiratory tract infections, bronchiectasis, lymphadenopathy, splenomegaly, and autoimmunity as the most common clinical features at diagnosis. These findings indicate the necessity of highlighting lymphoproliferative, gastrointestinal, and autoimmune manifestations alongside warning signs in the assessment for predicting immunodeficiency. The same meta-analysis underscored the high prevalence of immune dysregulation-associated manifestations, such as GLILD and enteropathy, which should be carefully evaluated alongside infections when assessing for primary immunodeficiency [18].

Although our mortality rate was low (6.3%), both deceased patients had underlying bronchiectasis and belonged to the infection-dominated cluster. These findings, albeit not statistically significant, reflect the established association between chronic lung complications and poor

Table 3. Comparison of peripheral blood cells according to phenotypes with high impact on clustering

Parameter	Infection (+)	Infection (–)	*p*	Autoimmunity (+)	Autoimmunity (–)	*p*	Lymphoproliferation (+)	Lymphoproliferation (–)	*p*
Leukocytes (/µl), mean ±SD (min-max)	6861.67 ±2663.98	3864.29 ±2027.73	0.010	5627.5 ±3200.51	6779.33 ±2278.24	0.699	6271.3 ±3155.09	5936.25 ±1554.61	0.699
Neutrophils (/µl), mean ±SD (min-max)	4522.08 ±2195.77	2377.14 ±1613.76	0.024	3641.88 ±2620.63	4460 ±1757.7	0.472	4160.43 ±2540.37	3685 ±1077.86	0.472
Lymphocytes (/µl), mean ±SD (min-max)	1711.67 ±699.7	1101.43 ±319.34	0.034	1411.25 ±521.53	1747.33 ±798.92	0.617	1536.96 ±706.67	1680 ±630.44	0.617
Hemoglobin (g/dl), mean ±SD (min-max)	13.58 ±2.46	12.84 ±1.72	0.466	13.58 ±1.94	13.24 ±2.71	0.955	13.43 ±2.24	13.37 ±2.67	0.955
Monocytes (/µl), mean ±SD (min-max)	428.75 ±157.76	242.86 ±90.68	0.006	360 ±181.32	415.33 ±144.46	0.518	398.26 ±176.9	353.75 ±124.66	0.518
Eosinophils (/µl), mean ±SD (min-max)	112.5 ±92.13	58.57 ±41.4	0.147	96.25 ±91.2	104.67 ±82.79	0.274	110.43 ±95.46	71.25 ±40.86	0.274
Platelets (/µl), mean ±SD (min-max)	221000.79 ±83000.14	145000.43 ±95000.90	0.048	182000.25 ±101000.44	228000.33 ±73000.18	0.666	207000.35 ±103.71	196000.5 ±34000.71	0.666

Table 4. Comparison of immunoglobulins and complement 3/4 according to phenotypes with high impact on clustering

Parameter	Infection (+)	Infection (–)	*p*	Autoimmunity (+)	Autoimmunity (–)	*p*	Lymphoproliferation (+)	Lymphoproliferation (–)	*p*
C3 (mg/dl), mean ±SD (min-max)	1.37 ±0.26	0.78 ±0.21	0.001	1.11 ±0.38	1.36 ±0.31	0.770	1.18 ±0.39	1.25 ±0.30	0.770
C4 (mg/dl), mean ±SD (min-max)	0.31 ±0.15	0.13 ±0.10	0.039	0.25 ±0.15	0.28 ±0.13	0.629	0.26 ±0.13	0.30 ±0.20	0.629
IgG (g/l), mean ±SD (min-max)	3.57 ±2.79	4.04 ±2.53	0.697	4.19 ±2.29	2.9 ±3.18	0.255	3.32 ±2.65	4.70 ±2.70	0.255
IgM (g/l), mean ±SD (min-max)	0.34 ±0.48	0.31 ±0.16	0.891	0.3 ±0.21	0.38 ±0.59	0.792	0.35 ±0.29	0.30 ±0.10	0.792
IgA (g/l), mean ±SD (min-max)	0.42 ±0.3	0.32 ±0.21	0.567	0.41 ±0.393	0.39 ±0.40	0.080	0.33 ±0.335	0.61 ±0.49	0.080
IgE (IU/ml), median (min-max)	1.5 (0.2-101)	1.5 (1.5-32.5)	0.906	1.5 (1.5-37.1)	1.5 (0.2-101)	0.432	1.5 (0.2-37.1)	1.75 (1-101)	0.432
IgG1 (g/l), mean ±SD (min-max)	3.75 ±2.591	3.04 ±1.7	0.615	3.98 ±2.47	2.8 ±2.47	0.787	3.72 ±2.67	3.40 ±2.04	0.787
IgG2 (g/l), mean ±SD (min-max)	1.45 ±0.97	0.87 ±0.59	0.281	1.49 ±0.98	1.04 ±0.81	0.826	1.3 ±1.07	1.40 ±0.64	0.826
IgG3 (g/l), mean ±SD (min-max)	0.23 ±0.16	0.12 ±0.06	0.195	0.21 ±0.11	0.22 ±0.22	0.170	0.18 ±0.09	0.28 ±0.22	0.288
IgG4 (g/l), mean ±SD (min-max)	0.08 ±0.04	0.06 ±0.005	0.398	0.08 ±0.050	0.06 ±0.006	0.403	0.08 ±0.05	0.06 ±.019	0.413

Table 5. Comparison of lymphocyte subsets according to phenotypes with high impact on clustering –

Parameter	Infection (+)	Infection (–)	*p*	Autoimmunity (+)	Autoimmunity (–)	*p*	Lymphoproliferation (+)	Lymphoproliferation (–)	*p*
$CD3^+$ T lymphocytes (%), mean ±SD (min-max)	72.99 ±14.25	76.68 ±10.66	0.536	74.90 ±13.55	72.59 ±13.56	0.659	74.3 ±13.68	72.93 ±13.35	0.812
$CD19^+$ B lymphocytes (%), mean ±SD (min-max)	12.36 ±9.2	12.20 ±8.15	0.967	10.56 ±7.26	14.34 ±10.24	0.250	12.19 ±9.01	12.68 ±8.88	0.896
$CD3^+CD8^+$ T lymphocytes (%), mean ±SD (min-max)	43.39 ±17.19	38 ±8.42	0.273	37.63 ±14.05	47.27 ±16.23	0.092	44.92 ±18.87	34.45 ±8.11	0.105
$CD3^+CD4^+$ T lymphocytes (%), mean ±SD (min-max)	34.4 ±13.96	41.22 ±10.34	0.247	39.23 ±13.14	31.93 ±12.89	0.154	33.94 ±12.2	42.6 ±15.33	0.139
$CD3^-CD16^+56^+$ NK cells (%), mean ±SD (min-max)	10.28 ±10.25	4.33 ±3.63	0.150	10.33 ±9.51	6.42 ±4.15	0.227	8.49 ±8.13	9.33 ±7.62	0.835
CD4/CD8 ratio (%), mean ±SD (min-max)	1.07 ±0.88	1.15 ±0.45	0.823	1.3 ±0.89	0.83 ±0.58	0.113	0.96 ±0.8	1.41 ±0.72	0.182
$CD3^+HLADR^+$ T lymphocytes (%), mean ±SD (min-max)	19.51 ±12.27	21.91 ±14.61	0.681	20.35 ±13.91	19.94 ±11.34	0.939	23.06 ±12.15	12.8 ±11.76	0.069
$CD8^+CD45RA^+$ (%), mean ±SD (min-max)	37.52 ±9.62	27.66 ±11.44	0.162	31.67 ±12.31	36.83 ±9.94	0.437	34.17 ±10.47	38.83 ±11.87	0.523
$CD4^+CD45RO^+$ (%), mean ±SD (min-max)	23.69 ±7.82	45.73 ±16.97	0.007	39.1 ±12.31	24.18 ±8.12	0.219	29.15 ±15.39	27.53 ±7.37	0.867
$CD8^+CD45RO^+$ (%), mean ±SD (min-max)	31.94 ±16.09	11.06 ±1.16	0.003	9.61 ±3.03	34.91 ±13.82	0.005	29.47 ±16.82	19.29 ±16.44	0.376
$CD4^+CD45RA$ (%), mean ±SD (min-max)	22.63 ±18.22	16.4 ±7.57	0.585	19.03 ±8.1	22.16 ±19.26	0.688	18.66 ±15.59	29.63 ±19.04	0.328
Naive B cells ($CD19^+CD27^-IgD^+$) (%), mean ±SD (min-max)	82.62 ±17.73	85.18 ±6.58	0.715	80.13 ±17.58	87.64 ±11.25	0.660	84.14 ±17	81.05 ±10.78	0.660
Unclass Switch Memory B cells ($CD19^+CD27^+$ IgD^+) (%), mean ±SD (min-max)	10.39 ±9.27	10.56 ±95.62	0.965	11.71 ±7.69	8.7 ±9.23	0.374	9.36 ±7.77	13.34 ±9.73	0.290
Class Switch Memory B cells ($CD19^+CD27^+IgD^-$) (%), mean ±SD (min-max)	22.22 ±2.11	2.11 ±2.32	0.949	2.43 ±2.23	1.85 ±1.14	0.700	1.93 ±1.87	2.87 ±2.25	0.574
AR B cells ($CD21^{low}CD38^{low}$) (%), mean ±SD (min-max)	11.85 ±9.34	9.78 ±7.5	0.628	13.82 ±9.1	7.10 ±6.88	0.047	10.19 ±8.27	15.69 ±10.4	0.222

outcomes in CVID [6, 20]. Similarly, lymphoid malignancy was detected in 6.3% of patients, consistent with prior studies reporting a 5-7% lymphoma prevalence in CVID cohorts [6, 7]. However, neither mortality nor malignancy showed a significant association with specific cluster groups, possibly due to the limited follow-up duration and sample size in our study.

Autoimmune cytopenias were the most frequent autoimmune manifestations in our cohort, with immune thrombocytopenia being the predominant subtype. These findings are consistent with previous studies reporting a strong association between autoimmune cytopenias, lymphoproliferation, and other non-infectious complications in CVID [4, 21, 22]. While gastrointestinal, granulomatous, and malignant complications were present in our cohort, no statistically significant correlation with autoimmunity was observed, likely due to limited sample size.

Immunophenotypic analyses revealed distinct patterns associated with clinical subgroups. Patients with autoimmunity demonstrated significantly higher frequencies of activated B cells ($CD21^{low}CD38^{low}$) and reduced $CD8^{+}$-$CD45RO^{+}$ T cell percentages, in line with previous studies suggesting dysregulation of memory T cell compartments and B cell activation as key contributors to autoimmunity in CVID [10, 12, 23]. Similarly, patients with infections exhibited increased leukocyte, neutrophil, monocyte, lymphocyte counts, and complement levels (C3, C4), potentially reflecting persistent immune activation in response to recurrent infections. Notably, memory $CD4^{+}$ T cells were significantly elevated in patients without infections, while $CD8^{+}CD45RO^{+}$ T cells were higher in those with infections, supporting the hypothesis that T cell memory alterations may influence infection susceptibility and disease phenotype [24, 25].

An intriguing finding was the association between older age at diagnosis and higher NK cell percentages, independent of infection status. Age-related expansion of NK cells has been documented [26, 27]. In addition, in a study where the clinical and phenotypic features of CVID among younger and older adults have been described, a higher CD4/CD8 T-lymphocyte ratio in the older cohort was revealed in flow cytometric analysis [28]. Our cohort's relatively young age distribution suggests that other immunological or environmental factors may contribute to this observation in CVID, warranting further investigation.

Allergic diseases remain an underrecognized component of CVID, with considerable variation reported across cohorts [20, 29]. Studies conducted on patients diagnosed with CVID have reported allergic diseases such as asthma, rhinitis, food allergy, and drug allergy. However, the rate of identifying triggering allergens was found to be lower than the presence of symptoms. The prevalence of allergic asthma and allergic rhinitis was reported to be 10% and 11%, respectively [29]. In another study involving 44 patients with CVID, allergic diseases were detected in 18 patients (40.9%) [14]. It remains unclear whether the differences observed across studies are due to variations in environmental exposures or due to the under-recognition of the potential for IgE-mediated diseases in CVID patients, which may lead to insufficient use of diagnostic skin testing for identifying triggering allergens. In our study, allergic manifestations were identified in 34.4% of patients, including asthma (18.8%), atopic dermatitis, and allergic rhinitis. Interestingly, allergic diseases were most frequent in Cluster 2, which was defined by a lack of lymphoproliferation. In Cluster 2, distinguished by frequent co-occurrence of infections and allergies, allergic phenotypes were identified in 50% of patients, with no evidence of lymphoproliferation. In the general population, the prevalence of asthma has been reported to range between 5.5% and 13.5%, varying by country, according to the Centers for Disease Control and Prevention (CDC) [30]. In our study, all asthma diagnoses preceded CVID diagnosis, emphasizing the importance of considering primary immunodeficiency in patients with severe or atypical allergic presentations. Although the relationship between allergy and CVID remains incompletely understood, altered T cell regulation, defective central tolerance, and microbial dysbiosis have been proposed as contributing factors [20].

Our study has several limitations. Its retrospective, single-center design may limit generalizability, and the small sample size reduces statistical power for subgroup comparisons. Furthermore, the absence of genetic testing precludes definitive conclusions regarding monogenic contributions to the observed phenotypes.

Despite these limitations, our findings provide valuable insights into the clinical and immunological heterogeneity of CVID. The identification of distinct clusters based on clinical and laboratory profiles highlights the potential utility of integrating phenotypic and immunophenotypic data for risk stratification and individualized patient management. In particular, the prominence of autoimmunity and lymphoproliferation in one cluster suggests that these features may serve as important markers for more complex disease courses.

In conclusion, our results underscore the importance of comprehensive clinical and immunological evaluation in CVID patients. Recognizing distinct subgroups, particularly those with autoimmune and lymphoproliferative complications, may facilitate earlier diagnosis, more targeted follow-up, and the development of personalized management strategies. Future prospective, multicenter studies with integrated genetic analyses are essential to validate our findings and further elucidate the pathophysiological mechanisms driving CVID heterogeneity.

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Disclosures

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