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ORIGINAL ARTICLE

# Common variable immunodeficiency and autoimmune diseases: A 10-year single-center experience

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***ABSTRACT***

**Objectives:** This study aimed to determine the frequency of autoimmune diseases (ADs) accompanying common variable immunodeficiency (CVID) and evaluate clinical and immunological features, organ manifestation, and effects on malignancy and mortality.

**Patients and methods:** The retrospective study was conducted with 85 patients (47 males, 38 females; median age: 38 years; range, 30 to 53 years) with CVID between January 2013 and January 2023. The patients were divided into two groups according to the presence of ADs: CVID patients with ADs [AD-CVID (+) group; n=36] and CVID patients without ADs [AD-CVID (–) group; n=49]. The clinical and immunological features of the groups were compared, and the effects on organ manifestations, malignancy development, and mortality were evaluated.

**Results:** The diagnostic delay in the AD-CVID (+) group was 84 months and was longer than that in the AD-CVID (–) group. The most common AD was cytopenia, particularly immune thrombocytopenic purpura. Splenomegaly was the most common organ manifestation. Sjögren syndrome was the most common rheumatic disease. There was no difference between the immunoglobulin levels and lymphocyte subgroup levels, whereas the class-switched memory B cell levels were lower in the AD-CVID (+) group. While malignancy, particularly non-Hodgkin lymphoma, was more common in the AD-CVID (+) group, no difference was observed in mortality between the groups.

**Conclusion:** Adult CVID patients with ADs have a longer diagnostic delay. Autoimmune conditions, particularly autoimmune cytopenias and inflammatory diseases, are much more common in patients with CVID than in the general population. Therefore, physicians' awareness of autoimmune manifestations in CVID patients should be increased to prevent delays in diagnosis.

***Keywords:*** Autoimmunity, cytopenia, immunodeficiency, rheumatic disease, splenomegaly.

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency, with an estimated incidence of 1 in 50,000 to 20,000.[1] Diagnostic criteria include serum immunoglobulin (Ig) G levels at least two standard deviations below the age-appropriate reference levels in individuals over four years of age, low serum IgA or IgM, accompanied by impaired or absent specific antibody production, and the exclusion of other causes of hypogammaglobulinemia.[2]

The pathogenesis of CVID is still unknown. The loss of B-cell function is a common immune defect in all CVID patients. This defect may also result from a deficiency of other cells that help in antibody production. In most cases, it is accompanied by a decrease in the number and percentage of class-switched memory B (cSMB)

cells and plasma cell loss.[3-6] These patients have a propensity for autoimmune and inflammatory conditions, potentially due to a defect in the standard mechanisms that allow tolerance to be established. Therefore, genetic mutations associated with autoimmunity should be considered, specifically in CVID patients with autoimmune conditions.[7]

Common variable immunodeficiency usually manifests with recurrent sinopulmonary infections. However, noninfectious autoimmune or inflammatory conditions are considerable and can sometimes be the first manifestation of CVID. These include lymphoid hyperplasia, granulomatous inflammation, gastrointestinal and pulmonary inflammatory disease, splenomegaly, and various forms of autoimmunity.[8,9] The CVID research community is working hard to elucidate the immune mechanisms underlying noninfectious conditions and develop more effective treatment strategies.[10]

The present study aimed to investigate the relationship between autoimmune diseases (ADs) and clinical features, immunological parameters, organ manifestations, malignancy development, and mortality in adult CVID patients, thus increasing the quality and duration of life of patients with early diagnosis and treatment. Another aim was to emphasize that immunodeficiencies should be kept in mind in patients with multiple autoimmune conditions refractory to treatment.

## PATIENTS AND METHODS

This retrospective study was conducted at the adult immunology and allergy clinic of the Necmettin Erbakan University Faculty of Medicine between January 2013 and January 2023. According to the diagnostic criteria of the European Society for Immunodeficiencies, 85 patients (47 males, 38 females; median age: 38 years; range, 30 to 53 years) diagnosed with CVID were included in the study.[11] Patients were divided into two groups according to the presence of accompanying ADs: CVID patients with ADs [AD-CVID (+) group; n=36] and CVID patients without ADs [AD-CVID (–) group; n=49]. Patients with gastrointestinal, skin, and ocular symptoms suspicious for AD who were under investigation and had no definite diagnosis were excluded from both groups (Figure 1). Accompanying ADs were identified in CVID patients and compared in terms of their clinical features, immunological parameters, and organ findings. Patients with a minimum follow-up

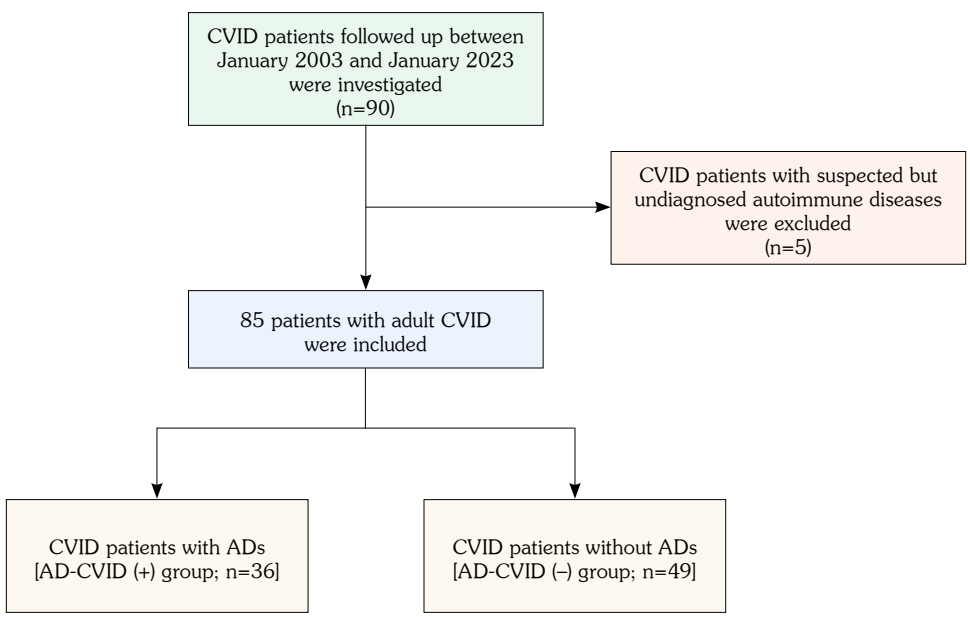


**Figure 1.** Flow chart of the study protocol. The inclusion and exclusion criteria were strictly applied throughout the screening.
CVID: Common variable immunodeficiency.

period of 10 years were evaluated in terms of malignancy development and mortality, and the relationship with ADs was determined. The study protocol was approved by the Necmettin Erbakan University Non-Pharmaceutical and Medical Device Research Ethics Committee (date: 01.09.2023, no: 2023/4473). The study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective data screening method of the study, the requirement for informed consent was waived by the ethics committee.

Data regarding the sex, current age, age at diagnosis, delay in diagnosis, reason for initial presentation, AD, malignancy development, and mortality of the patients were collected from the electronic hospital records and the archive system. A diagnostic delay was defined as the time from the onset of frequent infections or the emergence of an AD until the diagnosis of CVID. Serum IgG, IgA, and IgM levels at the time of diagnosis, and lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ ratio, $CD19^+$, $CD16^+$ $CD56^+$, and cSMB cells) were recorded. The CVID patients were clinically followed up every three to four weeks at the time of presentation for treatment. Laboratory and radiological follow-up took place every three months, and recent abdominal ultrasonography, superficial tissue ultrasonography for lymphadenopathies, and thoracic high-resolution computed tomography were evaluated for organ involvement.

Serum Ig levels were determined using a nephelometry analyzer (Siemens BN™ II System; Siemens Healthcare GmbH, Erlangen, Germany). Normal ranges for serum IgG, IgG, and IgA were 7-16 g/L, 0.46-3.04 g/L, and 0.7-4 g/L, respectively.

The peripheral blood samples (2 mL) of 85 CVID patients, drawn into anticoagulant EDTA (ethylenediaminetetraacetic acid) tubes at admission, were tested within 6 h. Peripheral blood lymphocyte subset numbers were measured via multicolor flow cytometry using a key panel. Cells were analyzed on a BD FACS Canto II Flow Cytometry System (BD Biosciences, San Jose, CA, USA). Lymphocyte subgroups were expressed as percentages, and the reference values were as follows: $CD3^+$ T cells=57-85; $CD3^+CD4^+$ T helper (Th) cells=30-61; $CD3^+CD8^+$ T cytotoxic cells= 12-42; $CD3^+CD19^+$ B cells=6-29; CD3-$CD16^+$ $CD56^+$ natural killer cells=4-25; $CD19^+CD27^+$IgD– cSMB cells=9.2-18.9.

### Statistical analysis

Data were analyzed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented as medians with the interquartile range ($25^{th}$-$75^{th}$ percentiles), and categorical variables were presented as frequency and percentage for each category. The Mann-Whitney U test was used to evaluate continuous data according to the presence of autoimmunity. Categorical variables were assessed using the Pearson's chi-square test or Fisher exact test. A p-value ≤0.05 was considered statistically significant.

## RESULTS

Of 85 patients, 24.7% presented with noninfectious causes. The median delay in diagnosis was 48 months. During follow-up, malignancy developed in seven (8.2%) patients, and 13 (15.3%) patients died (Table 1). Mortality was mostly due to sepsis secondary to infections (61.5%), followed by malignancy (38.5%).

Autoimmune diseases were associated with 36 (42.4%) of CVID patients, with one AD found in 24 (66.6%) patients and more than one AD found in 12 (33.3%) patients (Table 1). The most common AD was autoimmune cytopenia (AIC). The most common cause of AIC was immune thrombocytopenic purpura (ITP; 12.9%). Rheumatic diseases were observed the second most common AD (11.8%). The most common rheumatic disease was Sjögren syndrome (SjS; 3.5%). Splenomegaly was the most common organomegaly (36.5%). Bronchiectasis was observed in 31.8% of the total patient population (Table 1).

The demographic, immunological, and clinical characteristics of AD-CVID (+) group and AD-CVID (–) group were compared. There was no difference between the groups in terms of sex. The median diagnostic delay in the AD-CVID (+) group was 84 months, which was significantly longer (p=0.01). In this group, noninfectious causes were more common at initial presentation (p=0.01). The serum IgG, IgM, and

**Table 1.** General characteristics of patients with common variable immunodeficiency (n=85)

| | n | % | Median | IQR |
|---|---|---|---|---|
| Type of application | | | | |
| Infectious | 64 | 75.3 | | |
| Non-infectious | 21 | 24.7 | | |
| Age (year) | | | 38 | 30-53 |
| Age at diagnosis (year) | | | 29 | 18-44 |
| Sex | | | | |
| Male | 47 | 55.3 | | |
| Female | 38 | 44.7 | | |
| Delay in diagnosis (month) | | | 48 | 13-114 |
| Presence of autoimmunity | 36 | 42.4 | | |
| Mono-autoimmunity | 24 | 66.6 | | |
| Poly-autoimmunity | 12 | 33.3 | | |
| Mortality | 13 | 15.3 | | |
| Autoimmunity-related diagnoses | | | | |
| Cytopenia | 15 | 17.6 | | |
| ITP | 11 | 12.9 | | |
| OIHA | 8 | 9.4 | | |
| Autoimmune neutropenia | 3 | 3.5 | | |
| Rheumatic disease | 10 | 11.8 | | |
| Thyroiditis | 7 | 8.2 | | |
| Lymphoma | 6 | 7.1 | | |
| IBD | 3 | 3.5 | | |
| Hepatitis | 2 | 2.4 | | |
| GLILD | 2 | 2.4 | | |
| Alopecia | 1 | 1.2 | | |
| Multiple sclerosis | 1 | 1.2 | | |
| Organomegaly | | | | |
| Splenomegaly | 31 | 36.5 | | |
| Hepatomegaly | 18 | 21.2 | | |
| Lymphadenopathy | 6 | 7.1 | | |
| Bronchiectasis | 27 | 31.8 | | |
| Malignancy | 7 | 8.2 | | |

IQR: Interquartile range; ITP: Immune thrombocytopenic purpura; OIHA: Autoimmune hemolytic anemia; IBD: Inflammatory bowel disease; GLILD: Granulomatous lymphocytic interstitial lung disease.

IgA levels and $CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ cell percentages were higher in the AD-CVID (+) group than in the AD-CVID (–) group but were not statistically significant. The cSMB cell levels were significantly lower in the AD-CVID (+) group (p=0.002). Splenomegaly and bronchiectasis were significantly higher in the AD-CVID (+) group (p=0.04 and p=0.03, respectively). Malignancy was significantly more common in this group, and non-Hodgkin lymphoma (NHL) was the most common malignancy (p=0.002). There was no significant difference in mortality between the groups (Table 2).

## DISCUSSION

This study investigated the development of ADs in CVID patients, their frequency, and related conditions. Groups with and without ADs were compared in terms of their clinical and immunologic features, organ manifestations, malignancy development, and mortality. It was found that the most common autoimmune condition was AIC, particularly ITP, the most common organ manifestation was splenomegaly, and the most common rheumatic disease was SjS. The delay in diagnosis was found to be longer in the AD-CVID (+) group. While no difference was

**Table 2.** Comparison of patients with CVID with and without ADs

| | Autoimmunity | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AD-CVID (–) group (n=49) | | | | AD-CVID (+) group (n=36) | | | | |
| Parameters | n | % | Median | IQR | n | % | Median | IQR | *p* |
| Age (year) | | | 38 | 29.5-49 | | | 40 | 31-55.5 | 0.58 |
| Age at diagnosis (year) | | | 27 | 17.5-42 | | | 31.5 | 18.5-50 | 0.25 |
| Delay in diagnosis (month) | | | 36 | 6.5-102 | | | 84 | 36-153 | **0.01** |
| Type of application<br>Infectious<br>Non-infectious | <br>42<br>7 | <br>85.7<br>14.3 | | | <br>22<br>14 | <br>61.1<br>38.9 | | | **0.01** |
| Sex<br>Male<br>Female | <br>27<br>22 | <br>55.1<br>44.9 | | | <br>20<br>16 | <br>55.6<br>44.4 | | | 0.96 |
| Splenomegaly | 13 | 26.5 | | | 18 | 50 | | | **0.04** |
| Hepatomegaly | 10 | 20.4 | | | 8 | 22.2 | | | 0.84 |
| Lymphadenopathy | 1 | 2 | | | 5 | 13.9 | | | 0.07 |
| Bronchiectasis | 20 | 40.8 | | | 7 | 19.4 | | | **0.03** |
| Mortality | 6 | 12.2 | | | 7 | 19.4 | | | 0.54 |
| Malignancy | 0 | 0 | | | 7 | 19.4 | | | **0.002** |
| IgA | | | 0.26 | 0.2-0.9 | | | 0.33 | 0.2-0.89 | 0.73 |
| IgM | | | 0.26 | 0.17-0.43 | | | 0.4 | 0.18-0.79 | 0.06 |
| IgG | | | 3.9 | 1.4-5.7 | | | 4.4 | 1.6-5.9 | 0.72 |
| Lymphocyte count | | | 1.7 | 1.1-2.2 | | | 1.4 | 0.9-2.3 | 0.63 |
| $CD3^+$ T cells | | | 77 | 70-84.5 | | | 77.5 | 72-87.7 | 0.70 |
| $CD3^+CD4^+$ T cells | | | 33 | 26.5-44.5 | | | 34 | 23.2-42.7 | 0.65 |
| $CD3^+$ $CD8^+$ T cells | | | 39 | 33-48.5 | | | 42 | 32.2-55 | 0.46 |
| $CD4^+/CD8^+$ ratio | | | 0.9 | 0.5-1.1 | | | 0.81 | 0.41-1.3 | 0.50 |
| $CD19^+$ B cells | | | 6 | 2-11 | | | 7 | 1.2-14 | 0.44 |
| $CD16^+56^+$ NK cells | | | 7 | 4-14.2 | | | 6 | 3-10.7 | 0.12 |
| $CD19^+27^+IgD^-$/cSMB | | | 4.2 | 1.6-11.8 | | | 1.5 | 0.8-7.4 | **0.002** |

CVID: Common variable immunodeficiency; ADs: Autoimmunity; IQR: Interquartile range; IgA: Immunoglobulin A; IgM: Immunoglobulin M; IgG: Immunoglobulin G; CD: Cluster of differentiation; NK: Natural killer; cSMB: Class-switched memory B.

observed between the Ig levels and lymphocyte subgroups, the cSMB cell level was lower in the AD-CVID (+) group. Malignancy, particularly NHL, was more common in the AD-CVID (+) group than in the AD-CVID (–) group, but no difference was observed in the mortality rate.

Common variable immunodeficiency is one of the most common innate immune defects and can lead to heterogeneous complications affecting all bodily systems.[12] Recurrent infections affect 70 to 80% of CVID patients and are the most well-known main symptom.[13] ADs are observed in approximately 30% (21 to 42%) of CVID patients and can sometimes be the first manifestation of the disease without infection.[8,14,15] Due to the chronicity and slow progression CVID patients with ADs, the age of onset and diagnosis is higher than in CVID patients without ADs, leading to a delay in diagnosis.[12] A diagnostic delay of six to eight years after initial presentation was reported in CVID patients, who are usually diagnosed in adulthood.[10] The current study detected concomitant ADs in 42.4% of CVID

patients. The median diagnostic delay was 84 months in the AD-CVID (+) group, which was higher than in the AD-CVID (–) group (p=0.01).

The pathogenic mechanism of autoimmunity in CVID is paradoxical. It has been suggested that the underlying cause of autoimmunity is based on the inability of these patients to eliminate microbial antigens, leading to alternative immune pathways and an excessive and chronic inflammatory response, damaging not only infected cells but also the surrounding tissue.[16-18] It is also thought that the high antigen load caused by recurrent or resistant infections causes autoimmunity by affecting tolerance through superantigens or molecular mimicry.[19] Although the mechanisms of ADs are still controversial, they likely involve central and peripheral tolerance disorders and defects in autoreactive T and B cells.[10] In CVID, defects in B cell maturation, CD21low B cells, and cSMB cell development can be encountered. As a result, the proportion of total B cells and cSMB cells is reduced.[20-24] The reduction or absence of B cell subsets is associated with various clinical manifestations, including AICs, splenomegaly, lymphadenopathy, and granulomatous diseases.[25]

The most common autoimmune manifestation of CVID was AICs, reported to be 700 times more common than in the general population.[9] Cytopenia occurs in 4 to 20% of patients. ITP is the most common AD accompanied by AIC.[4,8] In CVID, ITP has been reported in 7 to 14% of patients, autoimmune hemolytic anemia in 4 to 7%, and autoimmune neutropenia in 1%.[14] Similarly, the most common autoimmune manifestation in the current study was AIC, at a rate of 17.6%. ITP was the most common AD accompanied by AIC, while autoimmune neutropenia was the least common cytopenia.

It was reported that splenomegaly is the most common organ abnormality in CVID patients with ADs, followed by hepatomegaly and lymphadenopathy.[12] Similarly, splenomegaly was the most common organ abnormality in the same patient group, while lymphadenopathy was the least common. A significant difference was found between those with and without ADs. It was reported in the literature that only one AD was found in 70.5% of CVID patients with ADs, and more than one AD was found in 29.5%.[12] In the present study, it was found that 66.6% of patients in the AD-CVID (+) group had a single AD, and 33.3% had multiple ADs, which supports the literature.

Infections are the most common pulmonary complication in CVID. However, 30 to 60% of patients have various forms of chronic inflammatory lung disease contributing to morbidity and mortality.[8,14,26] Bronchiectasis is the most common chronic lung disease in patients with CVID. The prevalence of bronchiectasis has been reported at different rates in various studies, ranging from 11.2 to 90%.[14,27] A meta-analysis including 55 studies reported the overall prevalence of bronchiectasis as 34%.[27] Granulomatous lymphocytic interstitial lung disease (GLILD), generally specific to CVID, develops in approximately 10% of patients.[28] In the current study, 31.8% of the patients had CVID accompanied by bronchiectasis. GLILD was present in 2.4% of the patients and was found to be lower than that reported in the literature. This was thought to be due to the limited possibilities of histopathological diagnosis and the patients' resistance to invasive approaches. The presence of GLILD in CVID was reported to cause a decrease in survival.[26] The fact that one of the CVID patients in the current study had GLILD, which resulted in mortality at a young age, supports this.

Rheumatoid arthritis (RA; 2.6%), SjS (ranging from <1% to 4.2%), systemic lupus erythematosus (<1%), and, more rarely, other rheumatic diseases can be observed in CVID patients.[29] Raynaud's phenomenon, Behçet's disease, familial Mediterranean fever, RA, ankylosing spondylitis, and eosinophilic granulomatosis with polyangiitis are other rheumatic diseases.[15,30] In this study, SjS was the most common rheumatic disease, at a rate of 3.5%. Rarely, RA and ankylosing spondylitis were each observed in two patients, and Behçet's disease, familial Mediterranean fever, systemic lupus erythematosus, eosinophilic granulomatosis with polyangiitis, and Raynaud's phenomenon were each observed in one patient.

While skin manifestations are common in rare subtypes of primary immunodeficiencies, they are rare in CVID. Alopecia totalis, lichen

planus, psoriasis, and vitiligo have been reported as case reports in CVID.[8,31] Only one patient presented with alopecia totalis in the current study. Autoimmune thyroiditis (ranging from <1% to 3.9%) and multiple sclerosis (ranging from <1% to 3.9%), which are other ADs in CVID, are rarely reported.[29] In the present study, the rates of autoimmune thyroiditis and multiple sclerosis were 8.2% and 1.2%, respectively.

Autoimmune gastrointestinal complications have been found at frequencies ranging from 11 to 67% in CVID patients.[12,32,33] Inflammatory bowel disease was reported at a frequency of 7%, celiac disease at 3.7%, pernicious anemia at 0.4%, autoimmune enteropathy at 1.6%, and autoimmune hepatitis at 2%.[34] In the present study, autoimmune gastrointestinal manifestations were found at a rate of 5.8%, and inflammatory bowel disease (3.5%) was the most common, followed by autoimmune hepatitis (2.4%). The difference between the rates was due to the study design, follow-up of the patients, and nonspecific histopathological features.[34]

In a group of studies evaluating serum Ig levels and autoimmunity in CVID, no correlation was found between Ig levels and autoimmune conditions,[35,36] while other studies reported a significant relationship, with elevated IgM levels.[8,30] In another study comparing lymphocyte subsets, the absolute lymphocyte, $CD3^+$ T cell, $CD4^+$ T cell, and $CD19^+$ B cell counts were significantly higher in CVID patients without autoimmune complications.[12] In the present study, similarly, the serum Ig levels were higher in the AD-CVID (+) group, but no statistically significant difference was found.

Immune system components are influenced by diseases, as well as treatment modalities. The cSMB cells and long-lived plasma cells are considered to originate from B cells activated by T follicular helper cells in the germinal center.[37] The human memory B cell compartment has memory B cell subsets differentiated from three different origins. The cSMB cells differ from their precursors in their requirements for survival signaling.[38] One study showed that belimumab, a monoclonal antibody that inhibits the BlyS (B-lymphocyte stimulator) used in the treatment of patients with systemic lupus erythematosus, did not affect memory B cell levels. The preservation of memory B cells was thought to be due to them not being dependent on BLyS for survival.[39] However, another study revealed that plasma cells in human subjects treated with rituximab, an anti-CD20 monoclonal antibody used in the treatment of ADs, can be both short- and long-lived.[40,41] Glucocorticoids have different effects on the immune system. They impair cytotoxic immune responses by downregulating interferon-gamma production and inhibiting the development of $CD8^+$ T cells and natural killer cells. Additionally, glucocorticoids have been shown to activate the immune system by increasing the activities of Th2, Th17, and Ig-producing B cells through their receptors.[42] In the present study, some of the patients in the AD-CVID (+) group received immunosuppressive and biologic therapies, and all CVID patients received Ig replacement therapy (IgRT). Patients in the AD-CVID (+) group who had not previously received immunosuppressive and biologic therapies did not require additional therapies during follow-up. This was probably due to the immunomodulatory effect of IgRT. However, it was reported that both corticosteroids and monoclonal antibody treatments do not affect cSMB cell levels.[39,42] In our study, similar to other studies,[30,36,43,44] the cSMB cell levels were significantly lower in the AD-CVID (+) group. It was also reported that low cSMB cell levels are associated with the development of autoimmunity in CVID.[25,45] Low cSMB cell levels were reported to be an independent risk factor in predicting AD, granulomatous findings, and splenomegaly.[43] Therefore, it may be used as a guide in the routine evaluation and follow-up of CVID and other B cell-derived diseases.[36]

Although IgRT is used at higher doses in a wide range of autoimmune and inflammatory conditions due to its immunomodulatory effects,[46] the main indication for this therapy in CVID is to provide lifelong replacement of antibody deficiency and prevent and treat recurrent infections.[47] Due to the success of IgRT in treating bacterial infections in CVID patients, life expectancy has increased; consequently, ADs and malignancies have gradually become

the main cause of morbidity and mortality.[14,48] It was reported that 14.7% of CVID patients with ADs develop malignancy during follow-up, with NHL being the most common.[35,49] In the current study, 8.2% of the patients in the AD-CVID (+) group developed malignancy, and NHL was the most common malignancy. In a large cohort in the USA, the risk of death in CVID patients with one or more noninfectious complications was found to be 11 times higher than in those with infection alone.[14] In the present study, although the rate of mortality was higher in the AD-CVID (+) group, it was not statistically significant. However, malignancy development was significantly higher in this group, supporting the literature. This suggests that the success of IgRT in preventing infectious complications leads to a higher incidence of noninfectious complications in CVID patients.

Autoimmunity becomes more complex and challenging to manage with immunodeficiency, resulting in immune dysregulation. ADs in CVID need special consideration, as they may prolong the diagnostic and therapeutic process.[12] AD relapses have been reported to be more frequent in CVID patients who do not receive maintenance IgRT. Therefore, IgRT helps prevent concomitant autoimmune complications and relapses in CVID patients.[50]

The most important limitation of this retrospective study was that the temporal relationship between CVID and the development of ADs could not be established. In addition, the inadequacy of invasive diagnostic methods in detecting organ manifestations, particularly in the lung, constituted another limitation.

In conclusion, autoimmune manifestations, particularly cytopenia and inflammatory diseases, are much more frequent in patients with CVID than in the general population. Therefore, patients with ITP, anemia, or multiple cytopenia should be screened for CVID. Early recognition of autoimmune conditions is essential for personalized treatment, reducing the complications associated with CVID and improving quality of life. Therefore, physicians should increase their awareness of the autoimmune manifestation of CVID patients to prevent a delay in diagnosis and provide early diagnosis and treatment.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Concept, design: F.S.A., F.Ç., Ş.A.; Data collection or processing: F.S.A., F.Ç., R.E., M.K.; Analysis or interpretation: F.S.A., R.E., M.K., E.Y.; Literature review: F.S.A., E.Y.; Writing: F.S.A., Ş.A.; Had primary responsibility for the final content: F.S.A. All of the authors have read and approved the final manuscript.

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