ORIGINAL ARTICLE

Noninfectious Complications in B-Lymphopenic Common Variable Immunodeficiency

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Abstract

Background: Common variable immunodeficiency (CVID) is considered the most symptomatic type of inborn errors of immunity in humans. Along with infectious complications, which have numerous consequences, noninfectious complications are a major challenge among CVID patients.
Methods: All CVID patients registered in the national database were included in this retrospective cohort study. Patients were divided into 2 groups based on the presence of B-cell lymphopenia. Demographic characteristics, laboratory findings, noninfectious organ involvement, autoimmunity, and lymphoproliferative diseases were evaluated.
Results: Among 387 enrolled patients, 66.4% were diagnosed with noninfectious complications and 33.6% with isolated infectious presentations. Enteropathy, autoimmunity, and lymphoproliferative disorders were reported in 35.1%, 24.3%, and 21.4% of patients, respectively. Some complications, including autoimmunity and hepatosplenomegaly, were reported to be significantly more frequent among patients with B-cell lymphopenia. As for organ involvement, the dermatologic, endocrine, and musculoskeletal systems were predominantly affected in CVID patients with B-cell lymphopenia. Among autoimmune manifestations, the frequency of rheumatologic, hematologic, and gastrointestinal autoimmunity was reported to be higher than that of other types of autoimmunity not associated with B cell-lymphopenia. Furthermore, hematological cancers, particularly lymphoma, were the most common type of malignancy. The mortality rate was 24.5%, and respiratory failure and malignancies were the most common causes of death, with no significant differences between the 2 groups.

Conclusion: Considering that some of the noninfectious complications might be associated with B-cell lymphopenia, regular patient monitoring and follow-up with proper medication (in addition to immunoglobulin replacement therapy) are highly recommended to prevent sequelae and increase patient quality of life.

Key words: Primary immunodeficiency. Inborn errors of immunity. Common variable immunodeficiency. Autoimmunity. Malignancy. Immune dysregulation.

Resumen

Antecedentes: La inmunodeficiencia común variable (IDCV) se considera el más sintomático error innato de la inmunidad en humanos. Las complicaciones infecciosas (que tienen numerosas consecuencias clínicas) son, junto a las complicaciones no infecciosas, un reto importante entre los pacientes con IDCV.
Métodos: Todos los pacientes con IDCV registrados en nuestra base de datos nacional se incluyeron en este estudio de cohortes retrospectivo. Los pacientes se dividieron en dos grupos en función de la presencia o ausencia de linfopenia de células B. Se evaluaron las características demográficas, los resultados de laboratorio, la afectación no infecciosa de diferentes órganos, la autoinmunidad y las enfermedades linfoproliferativas.
Resultados: De los 387 pacientes incluidos, el 66,4% fueron diagnosticados de complicaciones no infecciosas y el 33,6% solo presentaron cuadros infecciosos. La enteropatía, la autoinmunidad y los trastornos linfoproliferativos se registraron en el 35,1%, el 24,3% y el 21,4% de los pacientes, respectivamente. Algunas complicaciones, como la autoinmunidad y la hepatoesplenomegalia, se reportaron de forma significativamente superior entre los pacientes con linfopenia de células B. En cuanto a la afectación de órganos, los sistemas dermatológico, endocrino y musculoesquelético se vieron afectados predominantemente en los pacientes con IDCV con linfopenia de células B. Entre las manifestaciones autoinmunes, se observó que la frecuencia de autoinmunidad con afectación reumatológica, hematológica y gastrointestinal era superior en comparación con otros tipos de autoinmunidad independientes de la linfopenia de células B. Además, los tumores hematológicos, en particular el linfoma, fue ligeramente el tipo más común de neoplasia maligna. A su vez, la tasa de mortalidad global fue del 24,5%. La insuficiencia respiratoria y los tumores malignos fueron reportados como la causa más común de muerte en nuestros pacientes sin diferencias significativas entre los dos grupos.
Conclusiones: Teniendo en cuenta que algunas de las complicaciones no infecciosas podrían estar asociadas con la linfopenia de células B, la monitorización y el seguimiento regular del paciente junto con el tratamiento adecuado (además de la terapia de reemplazo de inmunoglobulinas) son recomendables para prevenir secuelas posteriores y aumentar la calidad de vida de los pacientes.

Palabras clave: Inmunodeficiencia primaria. Errores innatos de la inmunidad. Inmunodeficiencia común variable. Autoinmunidad. Malignidad. Disregulación inmune.

Summary box

- **What do we know about this topic?**
  Peripheral B cells in CVID patients range from normal counts in most cases to B lymphopenia in a minority, indicating defects of early B-cell development in the latter.
- **How does this study impact our current understanding and/or clinical management of this topic?**
  Our findings indicated that noninfectious complications including autoimmunity and lymphoproliferative manifestations affecting the dermatologic, endocrine, and musculoskeletal systems are associated with B-cell lymphopenia in CVID patients.

Introduction

Common variable immunodeficiency (CVID) is the most common symptomatic form of inborn errors of immunity (IEI) [1] and was first reported in 1945 by Sanford et al [2]. A heterogeneous immune defect, CVID is characterized by decreased serum immunoglobulin levels [3], reduced or absence of specific antibody production, and normal or low B-lymphocyte counts [4-6]. The prevalence of CVID is estimated at 1:50 000 to 1:25 000 [7]. Although CVID can occur at any age, this rare disease frequently appears in childhood or early adulthood [1,8]. Furthermore, men and women are equally affected [9]. Of note, given the gradual development of humoral immunity and the probability of transient hypogammaglobulinemia in infancy, a diagnosis of CVID should not be considered in patients aged <4 years [5]. The fact that CVID patients experience failure in B-cell differentiation into functional Ig-secreting plasma cells means that it is categorized mainly as comprising intrinsic B-cell defects. However, some patients experience a defect in other types of lymphocytes and immune components that play a significant role in the normal antibody response [7].

CVID has a wide spectrum of clinical presentations, including recurrent infections and noninfectious complications

such as autoimmunity, gastrointestinal inflammatory disease, liver disease, lymphoid hyperplasia, granulomatous disease, cytopenia, progressive lung disease, and cancer [10-12]. Noninfectious manifestations may be the first or predominant clinical presentation of CVID [13]. Approximately 20%-30% of CVID patients develop different forms of autoimmunity (as the most commonly reported form of noninfectious complications), such as juvenile rheumatoid arthritis, autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE), alopecia areata, vitiligo, pernicious anemia, and autoimmune thyroiditis [14]. The risk of death is 11 times higher in CVID patients with noninfectious complications [11,12,15]. In addition, immunoglobulin replacement therapy, which is the standard treatment approach for CVID patients, cannot prevent or diminish most noninfectious manifestations [10,11]. Therefore, mortality and morbidity are major concerns amongst CVID patients with noninfectious complications [5,12,16].

CVID is a heterogeneous group of antibody defects in which the B-lymphocyte populations are mostly dysregulated. Although B-cell count as a key diagnostic marker has been discussed in detail, few studies have evaluated in depth CVID patients with low total B-cell counts and expected early B-cell developmental defects. Here, an updated clinical spectrum of noninfectious complications was compared between 2 groups, namely, CVID patients with B-cell lymphopenia and without B-cell lymphopenia. This study compares the diverse characteristics of CVID cases with early B-cell defects and those of patients with abnormalities in late B-cell developmental stages. Both types are currently labeled with the same diagnosis.

Material and Methods

Patients

This retrospective cohort study was based on the records of all registered CVID patients [17-29] who were referred to and diagnosed and treated in the research center for immunodeficiencies at the Children's Medical Center, which is affiliated to Tehran University of Medical Sciences, Iran. CVID patients were identified and managed (immunoglobulin replacement therapy, prophylactic antibiotics, targeted treatments) according to signs and symptoms linked with the syndrome based on the national IEI consensus [20,30], the European Society for Immunodeficiencies (ESID) diagnostic criteria [31], and The Middle East and North Africa Diagnosis and Management Guidelines for IEI [32]. Symptomatic patients with reduced IgG and IgA and/or low serum IgM levels were included. Other causes of hypogammaglobulinemia were considered exclusion criteria in patients aged >4 years with a weak antibody response to vaccines or low switched memory B cells and no evidence of profound T-cell deficiency. Patients with normal responses to vaccines who had low switched memory B cells and lack of isohemagglutinin were also considered to have CVID. The present study was approved by the Ethics Committee of the Tehran University of Medical Sciences, and written informed consent was obtained from the patients and/or their parents.

Clinical Evaluation and Classification

We designed a comprehensive questionnaire, which was completed by the patients. The data recorded included age at clinical presentation, age at diagnosis, family history, consanguinity, autoimmunity, enteropathy, lymphoproliferation, malignancy, medications, last follow-up, and laboratory findings. Clinical phenotyping was performed using a standard method of phenotype subdivision that has been shown to correlate with quality of life and morbidity in patients with infections only and noninfectious phenotypes [12,33]. The evaluation also involved a complete blood count, lymphocyte subpopulations, serum Ig levels, specific antibody response, pulmonary function test (PFT), and high-resolution computed tomography (HRCT) scan, as previously described [28,34-40]. Immunologic tests were repeated for each patient every 6 months during routine follow-up visits after diagnosis to evaluate progression of their antibody deficiency. Patients were classified according to the absolute count of total peripheral B cells at the time of diagnosis and before initiation of treatment as having B lymphopenia (Group 1, <2 standard deviations of their normal age and >2% of circulating lymphocytes cells) and normal B-cell counts (Group 2) based on the age-standard ranges at the Research Center for Immunodeficiencies as the tertiary referral center using the previously described method [41,42]. Age-matched B-cell reference levels were as follows: 4-8 years, 300-1000/μL; 8-12 years, 200-500/μL; 12-18 years, 150-500/μL; and >18 years, 150-500/μL.

Statistical Analysis

The statistical analysis of this retroactive cohort study was performed using IBM SPSS Statistics for Windows (version 22.0, IBM Corp.) and R studio (version 4.1.3). The statistical analysis was based on parametric and nonparametric assumptions. The Kolmogorov-Smirnov test was conducted to determine the normality of the distribution. The χ^2 test and Fisher exact test were used to compare categorical variables based on a 2 × 2 table. The numerical variables were compared using the Mann-Whitney test or Kruskal-Wallis test and their parametric equivalents.

Results

Demographic Characteristics

The cohort comprised 387 patients diagnosed with CVID (222 male and 165 female, Table 1) in the Iranian national IEI registry. The median (IQR) ages of the patients at disease onset and at the time of the study were 2.0 (0.5-8.0) years and 25.0 (14.0-35.0) years, respectively. The median age of the patients at the time of the diagnosis was 10.0 (3.0-21.0) years. Overall, 70% of patients were diagnosed before age 18 years. Among the 387 patients, 215 (55.6%) were born to consanguineous families. Based on the B-cell count at the time of diagnosis, 168 patients were classified in Group 1, with low B-cell lymphopenia. Despite a similar age at onset and diagnosis, CVID patients with B lymphopenia (Group 1) had a significantly higher median age at the time of the study (27.0

Table 1. Demographic Data of the 387 CVID Patients With B Lymphopenia and Normal B Cells.

Parameter	All CVID patients (N=387)	CVID with B lymphopenia (n=168)	CVID with normal B cells (n=219)	*P* Value[a]
Sex ratio (male/female)	222/165	98/70	124/95	.73
Consanguinity, No. (%)	215 (55.6%)	102 (60.7%)	113 (51.6%)	.07
Family history of IEI, No. (%)	47 (12.1%)	19 (11.3%)	28 (12.8%)	.65
Median (IQR) age of patients at baseline, y	25.0 (14.0-35.0)	27 (18.0-38.0)	22 (12.2-32.7)	.02
Median (IQR) age at onset of symptoms, y	12.0 (0.5-8.0)	2.0 (0.5-9.0)	2.0 (0.5-8.0)	.89
Median (IQR) age at diagnosis, y	10.0 (3.0-21.0)	10.0 (4.0-26.2)	9.0 (2.6-19.0)	.13
Dead/Alive, No.	82/252	42/103	40/149	.10

Abbreviation: CVID, common variable immunodeficiency; IEI, inborn errors of immunity.
*$P<.05$, statistically significant.

Table 2. Immunologic Profile and Laboratory Data Comparison Between CVID Patients With B-Cell Lymphopenia and Patients With Normal B Cell Values.[a]

Laboratory finding	All CVID patients (N=387)	CVID with B lymphopenia (n=168)	CVID with normal B cells (n=219)	*P* value[b]
IgG, mg/dL	220 (50-470)	198.0 (29.5-493.0)	229.5 (71.2-440.5)	.40
IgA, mg/dL	9.5 (1.8-37.0)	9.0 (0.7-36.0)	10.5 (2.0-40.0)	.17
IgM, mg/dL	25.0 (8.5-50)	24.0 (8.0-53.0)	25.0 (9.0-50.5)	.96
Neutrophils, %	54.0 (41.0-67.0)	57.0 (44.0-68.0)	53.0 (37.2-65.0)	.03
Neutrophils/μL	3848.0 (2475.0-6014.0)	3914.3 (2377.0-6545.3)	3776.0 (2720.0-5636.4)	.83
Lymphocytes, %	35.0 (24.3-50.0)	30.5 (21.0-46.0)	38.0 (27.0-52.0)	.002
Lymphocytes/μL	2498.4 (1704.0-4221.5)	2224.8 (1555.0-3503.2)	2717.2 (1907.5-4694.0)	.003
$CD3^+$ T cells, %	74.0 (64.0-83.0)	82.0 (71.0-88.0)	69.0 (60.0-77.0)	<.001
$CD3^+$ T cells/μL	1778.4 (1244.8-2998.3)	1632.3 (930.0-2839.0)	1971.8 (1299-3073.6)	.04
$CD4^+$ T cells, %	32.0 (23.0-42.0)	32.0 (19.0-44.0)	33.5 (25.0-42.0)	.18
$CD4^+$ T cells/μL	771.8 (433.7-1349.0)	626.5 (339.7-1101.2)	954.6 (600.7-1647.7)	<.001
$CD8^+$ T cells, %	35.0 (25.0-50.0)	41.0 (31.0-56.0)	30.0 (22.2-42.0)	<.001
$CD8^+$ T cells/μL	889.4 (549.9-1425.2)	890.8 (483.6-1567.2)	888.0 (564.8-1317.0)	.95
CD19 lymphocytes, %	9.0 (4.0-17.0)	4.0 (2.0-6.0)	16.0 (11.5-23.0)	<.001
CD19 lymphocytes/μL	210.9 (79.3-493.6)	73.4 (36.1-144.0)	445.7 (258.8-915.8)	<.001
CD16 lymphocytes, %	7.0 (5.0-11.0)	7.0 (4.0-10.4)	7.4 (5.0-12.0)	.54
CD16 lymphocytes/μL	182.2 (105.4-345.3)	154.4 (64.4-292.4)	217.8(140.0-418.7)	.02
CD21 lymphocytes, %	4.7 (2.07-8.7)	2.9 (0.4-6.5)	5.7(2.1-12.7)	.08
CD21 lymphocytes/μL	3.6 (0.7-9.8)	1.05 (0.1-4.6)	7.6(2.1-12.8)	.03

[a]Values are shown as median (IQR).
[b]$P<.05$, statistically significant.

[18.0-38.0] years) than those with normal B cells (Group-2, 22.0 [12.2-32.7] years, $P=.02$).

Laboratory Features

The immunological profile of CVID patients is summarized in Table 2. Compared to patients with normal B-cell values, CVID patients with B lymphopenia had significantly increased percentages of neutrophils (53.0% [37.2%-65.0%] vs 57.0% [44.0%-68.0%], $P=.03$), $CD3^+$ T cells (69.0% [60.0%-77.0%] vs 82.0% [71.0%-88.0%], $P<.001$), and $CD8^+$ T cells (30.0% [22.2%-42.0%] vs 41.0% [31.0%-56.0%], $P<.001$). In contrast, in patients with B-cell lymphopenia, significantly lower values were recorded for absolute counts of $CD3^+$ T cells (1971.8 [1299-3073.6] vs 1632.3 [930.0-2839.0]/μL, $P=.04$), $CD4^+$ T cells (954.6 [600.7-1647.7] vs 626.5 [509.7-1101.2]/μL, $P<.001$), and $CD16^+$ lymphocytes (217.8 [140.0-418.7] vs

154.4 [64.4-292.4]/μL, *P*=0.02) than in patients with normal B-cell counts. Similarly, significantly lower values were also recorded among patients with B-cell lymphopenia for total lymphocyte percentages (38.0% [27.0%-52.0%] vs 30.5% [21.0%-46.0%], *P*<.001) and absolute counts (2717.2 [1907.5-4694.0] vs 2224.8 [1555.0-3503.2]/μL, *P*<.001). Although absolute counts of $CD21^+$ lymphocytes were lower in Group 1 than in the group with normal B-cell values (1.05 [0.1-4.6] vs 7.6 [2.1-12.8]/μL, *P*=.03), surprisingly, the percentage of this B-cell subpopulation did not differ significantly between the 2 groups (*P*=.08, Table 2).

Clinical Phenotyping and Organ Involvement

Among 387 CVID patients, 130 cases (33.6%) developed only infectious complications and 257 patients (66.4%) developed noninfectious complications. The most common noninfectious presentations were enteropathy (35.1%, n=136), autoimmunity (24.3%, n=94), and lymphoproliferation (21.4%, n=83). Of note, in patients with B lymphopenia, higher frequencies were recorded for all noninfectious phenotypes (73.8% vs 60.7%, *P*<.001) and autoimmune phenotypes (31.5% vs 18.7%, *P*=.003) than in patients with a normal B-cell count (Table 3). Considering the affected organ according to clinical phenotype, gastrointestinal complications (58.9%, n=228) were predominant in all CVID patients. Expectedly, hematologic complications (25% vs 13.7%, *P*<.001), musculoskeletal complications (10.7% vs 5%, *P*=.03), dermatologic complications (39.3% vs 24.2 %, *P*<.001), and endocrine complications (11.3% vs 5.5%, *P*=.03) were more frequent in Group 1. The frequency of cardiovascular complications (11.3% vs 5.9%, *P*=.05) was also higher in patients with B lymphopenia, although this difference was not significant (Table 4).

Autoimmune and Lymphoproliferative Complications

The clinical spectrum of autoimmune disease among selected 94 CVID patients was wide and included both hematologic autoimmunity (30.8%, n=29) and organ-specific autoimmunity (87.2%, n=82). Of note, some patients presented more than 1 type of autoimmunity. In this regard, organ-specific autoimmunity included rheumatologic autoimmunity (32%, n=30), gastrointestinal autoimmunity (24%, n=23), dermatologic autoimmunity (19.1%, n=18),

Table 3. Comparison of Clinical Phenotypes Between CVID Patients With B Lymphopenia and Patients With Normal B Cell Values.

Parameter	All CVID patients (N=387)	CVID with B lymphopenia (n=168)	CVID with normal B cells (n=219)	*P* Value[a]
Infection only	130 (33.6)	44 (26.2)	86 (39.3)	<.001
Noninfectious complications	257 (66.4)	124 (73.8)	133 (60.7)	<.001
Autoimmunity	94 (24.3)	53 (31.5)	41 (18.7)	.003
Lymphoproliferation	83 (21.4)	39 (23.2)	44(20.1)	.45
Enteropathy	136 (35.1)	61 (36.3)	75 (34.2)	.67
Allergy	73 (18.9)	39 (23.2)	34 (15.5)	.05
Malignancy	28 (7.2)	14 (8.3)	13 (5.9)	.35

**P*<.05, statistically significant.

Table 4. Specific Organ Involvement Between CVID Patients With B Lymphopenia and Patients With Normal B Cell Values.

Parameter	All CVID patients (N=387)	CVID with B lymphopenia (n=168)	CVID with normal B cells (n=219)	*P* Value[a]
Cardiovascular complications	32 (8.3%)	19 (11.3%)	13 (5.9%)	.05
Hematologic complications	72 (18.6%)	42 (25%)	30 (13.7%)	.004
Musculoskeletal complications	29 (7.5%)	18 (10.7%)	11 (5%)	.03
Neurologic complications	71 (18.3%)	31 (18.5%)	40 (18.3%)	.96
Dermatologic complications	119 (30.7%)	66 (39.3%)	53 (24.2%)	.001
Endocrine complications	31 (8.0%)	19 (11.3%)	12 (5.5%)	.03
Noninfectious gastrointestinal complications	228 (58.9%)	100 (59.5%)	128 (58.4%)	.83
Rheumatoid complications	67 (17.3%)	34 (20.2%)	33 (15.1%)	.18
Complications affecting multiple sites	259 (67%)	120 (71.4%)	139 (63.5%)	.09

**P*<.05, statistically significant.

endocrine autoimmunity (6.3%, n=6), and neurological autoimmunity (5.3%, n=5). ITP and AIHA were the most common types of hematologic autoimmunity in CVID patients (n=25 and n=15, respectively). Surprisingly, there were no sex differences in the prevalence of autoimmunity (Figure 1). However, the frequency of hematologic autoimmunity, especially AIHA, was higher in patients with B-cell lymphopenia than in those with normal B cells, although these differences were not significant. Moreover, autoimmune neutropenia (n=1), SLE (n=3), autoimmune vasculitis (n=3), juvenile dermatomyositis (n=1), and growth hormone deficiency (n=1) were only documented in Group 1 patients with B-cell lymphopenia (Table S1).

Splenomegaly, hepatomegaly, and granulomas were found in 26.1% (n=101), 17.3% (n=67), and 2.06% (n=8) of the cohort, respectively. The most common sites of granulomas identified by biopsies included the skin (n=3, 37.5%), liver (n=2, 25%), and lung (n=2, 25%). Other locations included the brain, lymph nodes, and spleen. There were no significant differences between granulomatous diseases in the 2 groups of patients in this study; however, hepatomegaly and splenomegaly (25.6% vs 11% [*P*<.001] and 36.9% vs 17.8% [*P*<.001], respectively) were significantly more frequent in Group 1 than in Group 2 (Table S2), indicating paradoxical lymphopenia in the periphery of these patients, together with lymphoid hyperplasia in their secondary lymphoid organs.

Other Clinical Manifestations

In our cohort, the prevalence of hematological diseases was 18.6% (n=72) overall. The most common hematological complications during course of the disease were anemia (68.0%, n=49), thrombocytopenia (52.7%, n=38), and neutropenia (41.6%, n=30). The frequency of hematological disease in patients with B-cell lymphopenia (25%, n=42) was significantly higher than in patients with normal B-cell values (13.7%, n=30, *P*=.004). Of note, higher values were recorded in Group 1 for bronchiectasis (33.9% vs 19.2%, *P*<.001), clubbing (24.4% vs 13.2%, *P*=.004), and sterile conjunctivitis (14.9% vs 7.8%, *P*=.02) (Table S3).

Twenty-eight patients (7.2%) had malignancies. The clinical spectrum was wide and included both hematologic cancers (85.7%, n=24) and solid tumors (14.3%, n=4). There were no sex differences in the prevalence of malignancy. The most common type of malignancy was non-Hodgkin lymphoma (50%, n=14), followed by Hodgkin lymphoma (28.5%, n=8). Two patients had leukemia. Gastric, breast, ovarian, and brain mass cancer were also observed (Table S4). There were no significant differences in the malignancy detected between the 2 groups of patients in this study.

Figure 1. Age distribution of noninfectious complications among patients with common variable immunodeficiency showing B lymphopenia and normal B-cell values.

Lung Function and Radiological Assessment

The results of PFTs were available for 65 patients at the time of diagnosis (age >6 years) and before therapy. The results were abnormal in slightly more than half of them (n=35, 53.8%), with an almost equal proportion of respiratory patterns: obstructive (FEV_1/FVC <70% in 12 patients, 18.4%), restrictive (defined as FVC% <80%, in 14 patients, 21.5%), and mixed (restrictive/obstructive, in 9 patients, 13.8%). Of note, all defective PFT patterns were slightly more frequent in Group 1 patients with B lymphopenia than in other CVID patients (Table S5).

HRCT indicated for 70 patients revealed abnormal findings in 52 (74.2%). The severity of bronchiectasis was as follows: severe in 9 patients (25.7%), moderate in 7 patients (20%), and mild in 19 patients (54.3%). The extent of bronchiectasis was as follows: 1-5 segments in 19 patients (54.4%), 6-9 segments in 8 cases (22.9%), and >9 segments in 8 cases (22.9%). The median Bhalla score was 19 (15-23). The Bhalla score was excellent in 43.2% of patients, and none of the patients were classified as having severe bronchiectasis. In the mild category, 66% of patients had moderate bronchiectasis, and 77.7% had 6 to 9 bronchopulmonary segments affected. Similar to the observed PFT result, abnormal HRCT findings were more common in patients in Group 1 (81.2% vs 68.4%, *P*=0.22, Table S5), as was a higher Bhalla score (20.2 vs 18.5, *P*=0.42). However, these differences were not statistically significant between the 2 CVID groups.

Mortality

A total of 82 patients (24.5%) died during follow-up (Table 1), and 53 (13.0%) patients did not attend their final visit. Respiratory failure was the most common cause of death among the deceased patients, accounting for 18.2% of cases (n=15). Other common causes of death were malignancy (n=7), neurological complications (n=5), gastrointestinal complications (n=3), and meningitis (n=3). The median age at onset of the disease among nonsurvivors was significantly lower than among survivors (1.0 [0.4-4.5] vs 2.0 [0.5-9.0] years, *P*=.02, respectively). The median diagnostic delay among nonsurvivors and survivors was 4.0 years (1.3-7.5) and 4.0 years (1.0-10.5), respectively. In nonsurvivors, the median duration of follow-up was 16 years (11.0-18.6). Moreover, among nonsurvivors, consanguinity was observed in 49 patients (59.8%). Despite differences in the B-cell count, the mortality rate was similar for Group 1 and Group 2 (28.9% vs 21.1%; *P*=0.1, Table 1). Although the Kaplan-Meier analysis revealed nonsignificant differences in the cumulative survival of the 2 groups (*P*=.36), we observed slightly more frequent earlier death in patients with normal B-cell counts (mainly in

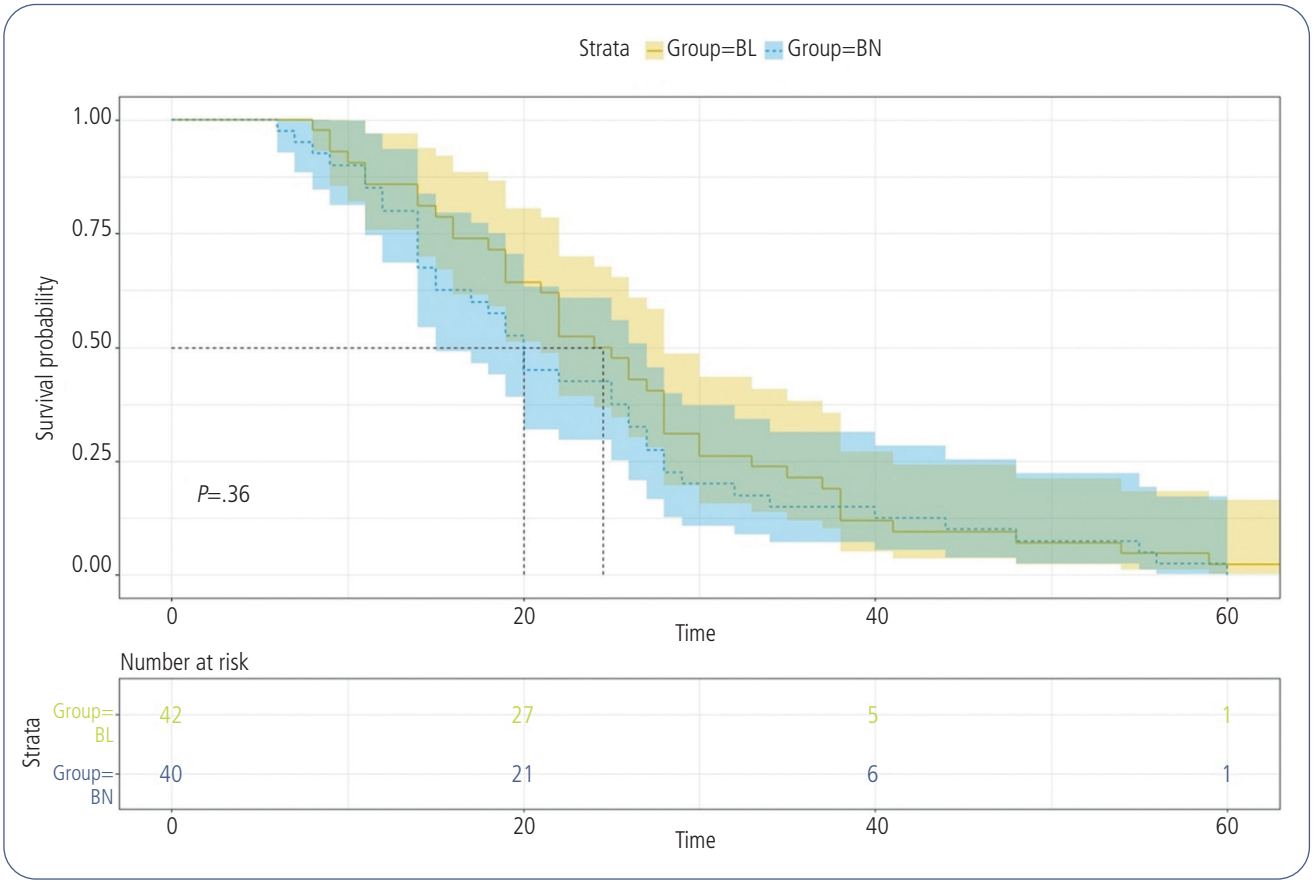

Figure 2. Kaplan-Meier graph depicting patient survival between common variable immunodeficiency patients with B-cell lymphopenia (BL) and with normal B-cell counts (BN).

patients aged 15-40 years, Figure 2); consequently, patients in group 1 were older at the time of the study, despite mortality rates being similar.

Discussion

CVID is defined as a heterogeneous type of IEI with a broad spectrum of immunological and clinical presentations. In the present study, we evaluated noninfectious complications in 387 enrolled CVID patients. CVID patients are characterized by a lower proportion of total and switched memory B cells than healthy controls [43]. Interestingly, the absence or reduced values of these B-cell subpopulations has been associated with specific clinical features, including splenomegaly, granulomatous disease, lymphadenopathy, and autoimmune cytopenia [44]. In our CVID cohort, noninfectious complications were recorded in 66.4% of the patients, a finding that is consistent with those of previous studies [45,46].

Autoimmune disorders are common in antibody defects, particularly CVID, affecting more than 20%-30% [47]. In the present study, the prevalence rate of autoimmune complications was 24.3%, the second most prevalent noninfectious clinical phenotype in our highly consanguineous, early-onset CVID cohort. Resnick et al [11] observed noninfectious complications in 68% of 473 CVID individuals, and 28.6% of these patients had hematologic or organ-specific autoimmune manifestations similar to those of the patients in our study. In contrast, Azizi et al [48] reported autoimmunity in 42.4% of patients diagnosed with a CVID-like disorder and monogenic defects, nearly double the autoimmunity reported in the present study. The prevalence of autoimmune cytopenia, or at least 1 type of autoimmune hematologic disease in 31 studies was 4.2%-44.7% [49]. Furthermore, ITP and AIHA have been reported to be the most common CVID-associated autoimmune disorders [49], a finding that is consistent with those of the current study, namely, that the prevalence of ITP and AIHA in B-lymphopenic CVID cases was 6.4% and 3.8%, respectively. Another report from the USIDNET registry demonstrated the prevalence of ITP and AIHA in CVID patients to be 7.4% and 4.5%, respectively [50], again, similar to the results of the present study. In this regard, in patients with B lymphopenia, the frequency of the autoimmune phenotype was higher than in patients with a normal B-cell count (31.5% vs 18.7%, P=.003).

Several studies have confirmed the association between rheumatologic disease and CVID [1,25]. It has been reported that rheumatologic disease affects up to 13% of patients with CVID [51-53]. Similarly, our data indicated that 17% of patients experienced rheumatologic complications; of these, 7.7% were diagnosed with different types of rheumatologic-related autoimmunity. RA, JIA, Sjögren syndrome, and SLE are the most frequent types of autoimmunity among these patients, as observed in our study [54]. Although the exact mechanisms of rheumatologic presentations in CVID patients are not completely clear, various autoimmune patterns have been suggested in affected patients, including the presence of autoantibodies, diminished number of regulatory T cells, elevated number of autoreactive B cells, reduced number of regulatory B cells producing IL-10, and cytokine production [55-57]. In contrast, Barsotti et al [58] could not find any correlation between the frequency of these immune cells and autoimmunity in CVID patients.

The reason for such a high rate of autoimmunity in B-lymphopenic CVID cases is still a matter for speculation. It has been proposed that specific autoreactivity checkpoints interrupt the expansion of self-reactive antibodies before the onset of somatic hypermutation and during B-cell maturation [59]. In fact, the most frequent type of immune dysregulation that renders CVID patients susceptible to autoimmune disorders is B-cell defects, as central tolerance can be disturbed owing to intrinsic defects and abolished B-cell receptor signaling, together with increased B cell–activating factor levels and, possibly, altered Toll-like receptor signaling, as well as defects in genes affecting multiple lymphoid subsets [60,63]. Above all, expanded $CD21^{low}$ B cells were repeatedly documented in mixed genetic CVID patients with autoimmunity [64-66]. In this regard, in the present study, absolute counts of $CD21^{+}$ lymphocytes were lower in patients with B-cell lymphopenia than in the normal B-cell group. Therefore, autoimmune diseases in B-lymphopenic CVID patients deserve special consideration, because dysfunctions of the immune system and immune dysregulation, along with continuous inflammation, can extend the procedure of recognition and treatment. Reduced central T-cell tolerance with the same molecular defects in negative selection and defective regulatory T-cell development can also accelerate the process of autoimmunity in affected patients. Other autoimmune manifestations in B-lymphopenic CVID in the present study affected the skin (4.6%), endocrine system (1.5%), and nervous system (1.2%) and were found to be uncommon yet limited to this group of patients, consistent with a previous systematic review [49]. Although most CVID patients have abnormalities in switched memory B cells and plasma cells, patients with B-cell lymphopenia may have other specific subpopulation defects. However, since the B-cell subpopulation can be affected by therapeutic modalities and was not available for deceased patients and for many patients at diagnosis, this analysis of the remaining few patients may be subject to bias, since we only focused on the main immune markers, which were investigated homogenously in all patients at diagnosis. Higher proportions of neutrophils and T cells, but lower counts of helper T cells, were among the significant phenotypes in CVID patients with B-cell lymphopenia. However, deeper investigation of B-cell subsets for newly diagnosed patients before initiation of treatment in future studies may elucidate the main disturbed developmental stage in these specific patients.

The prevalence of CVID-associated complications, including lymphoproliferative disease, has been shown to vary between countries [67]. Lymphoproliferative disease was reported in 21.4% of the 387 CVID patients included in this study, that is, more than in a recent adult-onset study [68]. In addition, the prevalence of splenomegaly as the most frequent type of lymphoproliferation in the present study (26.1%) was approximately half that of the outbreak reported in the EUROclass trial (40.5%) [69]. Furthermore, there was a significant difference between the prevalence of hepatosplenomegaly in B-lymphopenic cases and patients with a normal B-cell count. This might indicate a developmental defect leading to the arrest of B-cell maturation within the

secondary lymphoid organ, particularly during germinal center formation, thus also explaining the reduced level of B cells in the peripheral blood of these selected groups of patients. In our cohort, the prevalence of malignancy was 7.2% (28 cases in 387 CVID patients), which is consistent with a previous systematic review and meta-analysis showing that 48 studies assessed malignancy and reported 790 cases among 8123 cases of CVID (9.7%). Five of these patients had 2 types of malignancy [70,71]. The incidence of malignant lymphoma around the world has been increasing at a rate of 3%-4% over the last 4 decades [72]. Malignant lymphoma has been reported to comprise 3.37% of all malignancies worldwide [72,73]. In contrast, the results of the current study indicated that lymphoma accounts for 78.5% of all malignancies in CVID patients (22 cases in 28 patients with cancer), with equal findings in B-lymphopenic individuals and patients with a normal B-cell count (11 cases each). In contrast, another study reported a 40.5% prevalence of lymphoma in sporadic CVID patients with mostly adult-onset disease [74]. Although early recognition and medical treatment of CVID have improved in recent years, epidemiological findings show a high frequency of fatal malignancy in these cases [75,76]. In this regard, the mortality rate among patients with malignancy was high in the present study (40.7%). To date, the exact pathological mechanisms underlying this high frequency are not fully specified; however, various mechanisms, including impaired clearance of oncogenic viruses, genetic predisposition, immune dysregulation, impaired genetic stability, and iatrogenic causes, are thought to contribute to the development of malignancies in CVID [74]. Nevertheless, our study suggested that this is independent of B-cell lymphopenia.

The gut is the largest lymphoid organ, containing the highest percentage of lymphocytes, which, along with other immune cells (including macrophages and dendritic cells), manage the balance of the mucosal immune system. This, in turn, is in close contact with antigens of microorganisms such as viruses, bacteria, and parasites. Any related dysfunctions regarding the regulatory mechanisms might result in inflammation and gastrointestinal diseases. Therefore, in IEI patients with dysfunction of cellular or humoral immunity, observing gastrointestinal complications is not beyond expectation. It has been reported that 5%-50% of IEI patients are diagnosed with some gastrointestinal complications [77]. Various clinical immunologists have reported a high incidence of gastrointestinal presentations in patients diagnosed with CVID, ranging from 20% to 60%. Most patients have transient or chronic diarrhea, and some are also diagnosed with malabsorption and weight loss [78]. Following previous data [79-82], the frequency of gastrointestinal complications in our study was about 58.9%, which was slightly higher among patients with B-cell lymphopenia. Some CVID patients might be diagnosed with inflammatory and/or autoimmune gastrointestinal disease, which is considered a major cause of both mortality and morbidity. It has been reported that the mortality risk among CVID patients who develop gastrointestinal complications is 2.8 times higher than in patients without these complications [83]. In accordance with this statement, 3.6% of patients in our study died from various types of gastrointestinal complications. CVID-related enteropathy is characterized by the absence of plasma cells, follicular lymphoid hyperplasia, prominent intraepithelial lymphocytosis, and villous blunting. Besides, immunoglobulin replacement therapy does not improve the manifestations of enteropathy, potentially explaining why the rate of gastrointestinal complications remains high despite regular immunoglobulin replacement therapy [84].

Immunoglobulin replacement therapy and long-acting antibiotics are usually prescribed for CVID patients at specific intervals during their lifetime. Although the above-mentioned treatment reduced the frequency of infections and increased the survival rate among affected patients, it does not seem to have had any protective effect on some noninfectious complications, including autoimmunity, malignancies, structural and functional lung disease, and gastrointestinal presentations. These complications should be considered important, since inflammatory and autoimmune conditions might increase the mortality and morbidity rate. The mortality rate in our study was about 24.5%. In line with previous studies, respiratory complications and lung failure were the most common causes of death in CVID patients. In this regard, bronchiectasis is a common respiratory problem that might result in serious medical complications. In our study, 25.6% of patients were diagnosed with bronchiectasis using HRCT. However, the incidence rate might vary between studies. In a recent study by Ho et al [7], bronchiectasis affected 32.3% of patients. In another study conducted by Busse et al [85], 42% of CVID patients who had recurrent pneumonia were diagnosed with bronchiectasis. It should also be noted that, although most patients are receiving immunoglobulin replacement therapy, some CVID patients still develop bronchiectasis, and the condition might be the consequence of decreased switched memory B cells and deteriorated antibody production [86], potentially explaining why bronchiectasis is significantly more common among patients with B-cell lymphopenia than among patients with normal B cells. Furthermore, various malignancies, especially lymphoma, increase the mortality rate in patients diagnosed with CVID [83]. In our study, 7 patients died from cancer, which was the second most common cause of death.

Cultural diversity in various regions of the world means that determinants such as the consanguinity rate are different. In this regard, a higher rate of certain inheritance patterns, for example, autosomal disease, can be predicted. Moreover, the different genetic backgrounds of the CVID cohort studied may be dependent on founder mutations associated with geographical distribution. On the other hand, in countries that implement more complete diagnostic protocols and have access to advanced laboratory equipment, CVID may be diagnosed earlier, thus leading to a reduction in diagnostic delay and proper management without complications. All these parameters should be considered before generalizing the findings of this study; therefore, B-cell lymphopenia should be further studied in other CVID cohorts worldwide in the future. One of the limitations of the current study was the lack of a genetics-based diagnosis. The evaluation of genetic findings may enable evaluation of B-cell lymphopenia in patients with normal B cells and can potentially suggest targeted treatment for a selected group of patients in future studies.

Conclusion

B-cell defects, cellular abnormalities, and immune dysregulation have been detected in CVID patients. As a result, a broad spectrum of clinical presentations—both infectious and noninfectious—are expected in a considerable proportion of patients diagnosed with this disease. As mentioned earlier, some of these complications, such as respiratory complications and autoimmunity, are correlated with an increased mortality rate, which is also more common in CVID patients with B-cell lymphopenia, and might be challenging for physicians to manage. In addition, these early B-cell developmental defects in CVID patients may significantly increase the chance of dermatologic, endocrine, and musculoskeletal complications, with negative consequences for patients' quality of life. Our findings can serve as a prognostic guide for physicians who suspect CVID in patients with a history of noninfectious complications. These findings can lead clinicians to consider CVID and request additional tests to improve diagnosis, thus reducing diagnostic delay, preventing progression to severe disease, and enabling better therapeutic approaches.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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