Non-Infectious 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, non-infectious complications are also a major challenge among CVID patients.

Methods: All registered CVID patients in the national database were included in this retrospective cohort study. Patients were divided into two groups based on the presence of B-cell lymphopenia. Demographic characteristics, laboratory findings, non-infectious organ involvements, autoimmunity, and lymphoproliferative diseases were evaluated.

Results: Among 387 enrolled patients, 66.4% were diagnosed with non-infectious complications; however, 33.6% had only 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 higher among patients with B-cell lymphopenia. Among organ involvement, 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 compared to other types of autoimmunity independent from the B cell-lymphopenia. Furthermore, hematological cancers, particularly lymphoma, were slightly introduced as the most common type of malignancy. Meanwhile, the mortality rate was 24.5%, and respiratory failure and malignancies were reported as the most common cause of death in our patients without significant differences between the two groups.

Conclusion: Considering that some of the non-infectious complications might be associated with B-cell lymphopenia, therefore, regular patient monitoring and follow-up along with proper medications (besides immunoglobulins replacement therapy) are highly recommended to prevent further sequels and increase the patients' quality of life.

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

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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 33,6% sólo presentaron cuadros infecciosos y el 66,4% fueron diagnosticados además de complicaciones no infecciosas. 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. Mientras tanto, 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) es recomendable 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.

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Introduction

Common variable immunodeficiency disorder (CVID) is the most common symptomatic form of inborn errors of immunity (IEI) [1], which was recognized in 1945 by Sanford and his colleagues [2]. This heterogeneous immune defect is characterized by decreased serum immunoglobulin (Ig) levels [3], reduced or absence of specific antibody production and normal or low B lymphocyte counts [4-6]. The prevalence rate of this disease is estimated at 1:50,000 – 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, due to the gradual development of humoral immunity and the probability of transient hypogammaglobulinemia in infancy, CVID should not be diagnosed before the age of four [5]. Given that CVID patients have failure in B cell differentiation into functional Ig-secreting plasma cells, it is categorized mainly as 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 non-infectious complications such as autoimmunity, gastrointestinal (GI) inflammatory disease, liver disease, lymphoid hyperplasia, granulomatous disease, cytopenia, progressive lung disease, and cancer[10-12]. Non-infectious manifestations may be the first or predominant clinical presentation of CVID patients [13]. Approximately 20-30% of CVID cases develop different forms of autoimmunity (as the most commonly reported form of non-infectious complications), such as juvenile rheumatoid arthritis (JRA), 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 who present non-infectious complications [11,12,15]. In addition, Ig replacement therapy, which is the standard treatment approach for CVID patients, cannot prevent or diminish the majority of the non-infectious manifestations [10,11]. Therefore, mortality and morbidity are the major concerns amongst CVID patients with non-infectious complications [5,12,16].

CVID is a heterogeneous group of defects in antibodies in which the B lymphocyte populations are mostly dysregulated. Although the B cell counts as a main diagnostic marker have been discussed in detail, few studies have deeply evaluated CVID patients with low total B cell counts and expected early B cell developmental defects. Here, an updated clinical spectrum of non-infectious complications was compared between two groups of CVID patients with and without B cell lymphopenia. This study illustrates the diverse characteristics of CVID cases with early B cell defects versus patients with abnormalities in late B cell developmental stages, which are currently labeled with the same disease diagnosis.

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Material and Methods

Patients

This retrospective cohort study was conducted on the records of all registered CVID patients [17-29] who were referred, diagnosed and treated in the research center for immunodeficiencies at the Children's Medical Center affiliated to Tehran University of Medical Sciences, Iran. CVID patients were identified and managed (Ig replacement therapy, prophylactic antibiotics, targeted treatments) according to signs/symptoms linked with the syndrome based on the national IEI consensus [20,30]. Based on this consensus, the European Society for Immunodeficiencies (ESID) diagnostic criteria [31] and The Middle East and North Africa Diagnosis and Management Guidelines for IEI [32] were considered. Symptomatic patients with a reduced level of IgG and IgA and/or low serum levels of IgM were included. Other causes of hypogammaglobulinemia were marked as exclusion criteria in patients with age >4 years, 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 cell and lack of isohemagglutinin were also considered as CVID. The present study was approved by the ethics committee of the Tehran University of Medical Sciences, and written informed consent was obtained from all patients and/or their parents.

Clinical evaluation and classification

A comprehensive questionnaire was designed and completed for all patients, including age at the clinical presentation, age of 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 which has been shown to correlate with the quality of life and morbidity among patients with infections only and non-infectious phenotypes [12,33]. Complete blood count, lymphocyte subpopulations, serum Ig levels, specific antibody response, pulmonary function test (PFT) and high-resolution computed tomography (HRCT) scan were performed and analyzed as previously described [28,34-40]. Immunologic tests were repeated for each patient every 6 months during routine follow-up visits after the time of diagnosis to evaluate the 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 to the B-lymphopenia (Group-1, <2 standard deviations of their normal age, yet >2% of circulating lymphocytes cells) and normal B cell counts (Group-2) based on the age-standard ranges in Research Center for Immunodeficiencies as the tertiary referral center using the previously described method [41,42]. Age-matched B cell reference levels included: 4-8 years: 300-1000/ul; 8-12 years: 200-500/ul; 12-18 years: 150-500/ul and >18 years: 150-500/ul.

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Statistical analysis

SPSS software (version 22, SPSS Inc., Chicago, IL, USA) and R studio (version 4.1.3) were used for the statistical analysis of this retroactive cohort study. Statistical analysis was performed based on parametric and non-parametric assumptions of the collected data. In this regard, the Kolmogorov-Smirnov test was conducted to estimate the normal distribution. For 2 × 2 categorical variable comparisons, the Chi-square test and Fisher's exact test were utilized. The numerical variables were compared by the Mann-Whitney U or Kruskal-Wallis H tests and the parametric equivalent of these comparisons.

Results

Demographic characteristics

In this cohort, 387 CVID patients (222 male and 165 female, **Table 1**) who were diagnosed at the Iranian IEI national registry were studied. The median (interquartile range, 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 under the age of 18. Among 387 patients, 215 (55.6%) patients 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 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 [18.0- 38.0] years) compared to those with normal B cells (Group-2, 22.0 [12.2-32.7] years, p=0.02).

Laboratory features

The immunological profile of CVID patients is summarized in **Table 2**. Compared to patients with normal B cells, CVID patients with B lymphopenia showed significantly increased percentages of neutrophils (53.0% [37.2–65.0%] vs. 57.0% [44.0–68.0%], p=0.03), $CD3^+$ T cells (69.0% [60.0–77.0%] vs. 82.0% [71.0–88.0%], p<0.001) and $CD8^+$ T cells (30.0% [22.2–42.0%] vs. 41.0% [31.0–56.0%], p<0.001). In contrast, in patients with B cells lymphopenia the absolute counts of $CD3^+$ T cells (1971.8 [1299–3073.6] vs. 1632.3 [930.0–2839.0] cell/μL, p=0.04), $CD4^+$ T cells (954.6 [600.7–1647.7] vs. 626.5 [509.7–1101.2] cell/μL, p<0.001) and $CD16^+$ lymphocytes (217.8 [140.0–418.7] vs. 154.4 [64.4–292.4] cell/μL, p=0.02) were significantly decreased compared to patients with normal B cell count. In line with these observations, the percentages (38.0% [27.0-52.0%] vs. 30.5% [21.0-46.0%], p<0.001) and absolute counts (2717.2 [1907.5–4694.0] vs. 2224.8 [1555.0–3503.2] cell/μL, p<0.001) of total lymphocytes were significantly decreased in patients with B cells lymphopenia compared to normal B cells group. Although absolute counts of $CD21^+$ lymphocytes were decreased in Group-1 compared to

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the normal B cells group (1.05 [0.1–4.6] vs. 7.6 [2.1–12.8] cell/μL, *p*=0.03), surprisingly the percentage of this B cell subpopulation was not significantly different between two groups (*p*=0.08, **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 non-infectious complications. The most common non-infectious presentations were enteropathies (35.1%, n=136), autoimmunity (24.3%, n=94) and lymphoproliferation (21.4%, n=83). Of note, in patients with B lymphopenia the frequency of all non-infectious phenotypes (73.8% vs. 60.7%, *p*<0.001) and autoimmune phenotype (31.5% vs.18.7%, *p*=0.003) were higher compared to patients with normal B cell count (**Table 3**). Considering the affected organ by different clinical phenotypes, GI complications (58.9%, n=228) were predominant in all CVID patients. Expectedly, hematologic complications (25% vs.13.7%, p<0.001), musculoskeletal complications (10.7% vs. 5%, p=0.03), dermatologic complications (39.3% vs.24.2 %, p<0.001) and endocrine complications (11.3% vs.5.5%, p=0.03) were more frequent in Group1. The frequency of cardiovascular complications (11.3% vs. 5.9%, p=0.05) was also higher in patients with B lymphopenia, but 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 (30.8%, n=29) and organ-specific autoimmunity (87.2%, n=82). Of note, some patients presented more than one autoimmunity. In this regard, organ-specific autoimmunity included rheumatologic autoimmunity (32%, n=30), gastrointestinal autoimmunity (24%, n=23), dermatologic autoimmunity (19.1%, n=18), endocrine autoimmunity (6.3%, n=6) and neurological autoimmunity (5.3%, n=5). ITP (n=25), and AIHA (n=15) were the most common hematologic autoimmunity in CVID patients. Surprisingly, there was no gender difference in the prevalence of autoimmunity (**Figure 1**). However, the frequency of hematologic autoimmunity, especially AIHA, was higher in patients with B-cell lymphopenia compared to those with normal B cells, but 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) only were 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 overall cohort, respectively. The most common sites of granulomas identified by biopsies included 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 two groups of patients in this study; however, hepatomegaly and splenomegaly [(25.6% vs. 11%, *p*<0.001) and (36.9% vs. 17.8%, *p*<0.001), respectively] were recorded significantly higher in Group 1

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compared to Group 2 (**Table S2**), indicating a paradoxical overall 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 disease was 18.6% (n=72) overall. Among the hematological complications during course of the disease, anemia (68.0%, n=49), thrombocytopenia (52.7%, n=38) and neutropenia (41.6%, n=30) were the commonest. The frequency of hematological disease in patients with B-cell lymphopenia (25%, n=42) was significantly higher than in patients with normal B cells (13.7%, n=30, p=0.004). Of note, bronchiectasis (33.9% vs. 19.2%, p<0.001), clubbing (24.4% vs.13.2%, p=0.004), and sterile conjunctivitis (14.9% vs.7.8%, p=0.02) were higher in Group-1 compared to patients with normal B cell count (**Table S3**).

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

Lung function and radiological assessment

Results of PFTs were available from 65 patients at the time of diagnosis (>6 years old) and before therapeutic intervention. Nearly half of them (n=35, 53.8%) had abnormal results with an almost equal proportion between obstructive (FEV1/FVC less than 70% in 12 patients, 18.4%) and restrictive (defined as FVC% less than 80%, in 14 patients, 21.5%), and mixed (restrictive/obstructive, in 9 patients, 13.8%) respiratory patterns. Of note, all defective PFT patterns were slightly more frequent in Group 1 patients with B lymphopenia compared with other CVID patients (**Table S5**).

High-resolution computed tomography (HRCT) was medically indicated for 70 patients, and abnormal findings were found in 52 (74.2%). The severity of bronchiectasis was as follows: severe in 9 cases (25.7%), moderate in 7 patients (20%), and mild in 19 cases (54.3%). The extent of bronchiectasis was as follows: 19 patients (54.4%) showed 1 to 5 segment(s), 8 cases (22.9%) showed 6 to 9 segments, and 8 cases (22.9%) showed more than 9 segments. In the evaluation of the Bhalla score, the median score of the patients was 19 (15-23). Of the patients, 43.2% of patients had excellent Bhalla score quality, whereas none of the patients showed a "serious" classification. In the "mild" category, moderate bronchiectasis severity was involved in 66% of patients, and 77.7% of them were found to have 6 to 9 bronchopulmonary segments. Similar to the observed PFT result, patients within Group 1 have a higher

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abnormality in the HRCT (81.2% vs. 68.4%, p=0.22, **Table S5**) and a higher level of Bhalla score (20.2 vs. 18.5, p=0.42) but these differences were not statistically significant between two CVID groups.

Mortality outcome

During the follow-up period, 82 (24.5%) cases died during the study period (**Table 1**), and 53 (13.0%) patients were unavailable at their final visit. Respiratory failure was the most common cause of death among the deceased patients, accounting for 18.2% (n=15) of the cases. Other common causes of death were malignancy (n=7), neurological complications (n=5), GI complications (n=3) and meningitis (n=3). The median age at onset of the disease among non-survivors was significantly lower than survivors, [1.0 (0.4-4.5) years vs. 2.0 (0.5-9.0) years, *p*=0.02], respectively. The median diagnostic delay among non-survivors and survivors was 4.0 (1.3- 7.5) years and 4.0 (1.0-10.5) years, respectively. In non-survivor patients, the median follow-up duration was 16 (11.0-18.6) years. Moreover, among non-survivors, consanguinity was observed in 49 patients (59.8%). Considering the B cell count of CVID patients, the mortality rate was similar between the studied Group-1 and Group-2 (28.9% vs. 21.1%; p=0.1, **Table 1**). Although Kaplan-Meier analysis revealed non-statistical differences in the cumulative survival of the two groups (*p*=0.36), we observed slightly higher earlier death in patients with normal B cell counts (mainly in the period of age 15-40 years, **Figure 2**), leading to prominent higher age at the time of study in patients in group 1 despite similar mortality rates.

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 non-infectious complications of 387 enrolled CVID patients. CVID patients depict a reduced proportion of total and switched memory B cells compared to normal controls [43]. Interestingly, the absence or reduced numbers of these B cell subpopulations have been associated with certain clinical features, including splenomegaly, granulomatous disease, lymphadenopathy, and autoimmune cytopenias [44]. In our CVID cohort, non-infectious complications have occurred in 66.4% of the patient, which is consistent with the previous studies [45,46].

Autoimmune disorders are incident in predominantly antibody defects, particularly CVID, in which more than 20–30% of affected patients tend to expand autoimmune manifestations [47]. In the present study, the prevalence rate of autoimmune complications was 24.3%, the second most prevalent non-infectious clinical phenotype in our highly consanguineous and early-onset CVID cohort. While Resnick et al. [11] observed non-infectious complications in 68% of 473 CVID individuals, and 28.6% of these patients had hematologic or organ-specific autoimmune manifestations similar to our study's findings. In contrast, Azizi et al. reported 42.4% of autoimmunity in CVID-like diagnosed patients with monogenic defects [48], nearly double the outbreak of autoimmunity reported in the present study. The prevalence of autoimmune cytopenia or at least one type of autoimmune hematologic disease in 31

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studies was between 4.2% to 44.7% [49]. Also, ITP and AIHA have been reported as the most common CVID-associated autoimmune disorders [49], which is consistent with the current study that the prevalence of ITP and AIHA in B-lymphopenic CVID cases were 6.4% and 3.8%, respectively. Another report from the USIDNET registry demonstrated the prevalence of ITP and AIHA in CVID patients was 7.4% and 4.5%, respectively [50], which is similar to the results of the present study. In this regard, in patients with B lymphopenia, the frequency of autoimmune phenotype (31.5% vs.18.7%, p=0.003) was higher compared to patients with normal B cell count.

Several studies confirmed the association between rheumatologic disease and CVID [1,25]. It has been reported that rheumatologic disease frequency in CVID patients is approximately up to 13% [51-53]. Similarly, our data indicated that 17% of patients suffered from rheumatologic complications, of which 7.7% were diagnosed with different types of rheumatologic-related autoimmunity. RA, JIA, Sjogren's syndrome, and SLE are the most frequent type of autoimmunity among these patients, which is also observed in our study [54]. Although the exact mechanisms of rheumatologic presentations in CVID patients have not been explicitly introduced, autoimmune immunologic patterns, 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, cytokines production abnormalities are reported among these patients [55-57]. In contrast, Barsotti et al. could not find any correlation between these immune cells' frequency and autoimmunity in CVID patients [58].

The reason for such a high rate of autoimmunity in B-lymphopenic CVID cases is still a matter of 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 immune dysregulation which makes susceptible CVID cases to autoimmune disorders are B cell defects, as the central tolerance can be disturbed due to intrinsic defects and abolished B cell receptor signalings together with increased B cell-activating factor (BAFF) levels, and possibly altered Toll-like receptor (TLR) 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 current study, absolute counts of $CD21^{+}$ lymphocytes were decreased in patients with B cells lymphopenia compared to the normal B cells group. Therefore, autoimmune diseases in B-lymphopenic CVID patients deserve special consideration because dysfunctions of the immune system and immune dysregulations along with continuous inflammation can extend the procedure of recognition and treatment. Central T cell tolerance reduction with the same molecular defects on negative selection and defective regulatory T cell development can also accelerate the process of autoimmunity in these patients. Other autoimmune manifestations in B-lymphopenic CVID cases in the present study include dermatologic (4.6%), endocrine (1.5%), and neurologic (1.2%) autoimmunities were found to be uncommon but still unique

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for this group of patients, which is consistent with previous systematic review study [49]. Although the majority of CVID patients have abnormalities in switched memory B cells and plasmacells, patients with B cell lymphopenia might 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 the time of diagnosis performing this analysis on the remaining few patients may bias the analysis, so we only focused on the main immune markers which were investigated homogenously in all patients at the time of diagnosis. Higher proportions of neutrophil and T cell but lower counts of helper T cells were among the significant phnotype in the CVID patients with B cell lymphopenia. However deeper investigation of B cell subsets for newly diagnosed patients before treatment initiation in future studies may elucidate the main disturbed developmental stage in these selected patients.

The prevalence of CVID-associated complications, including lymphoproliferative disease, has been shown to vary among countries [67]. The lymphoproliferative disease was reported in 21.4% of the 387 CVID patients included in this study, which is more than the findings of a recent adult-onset study [68]. In addition to this, the prevalence of splenomegaly, as the most frequent type of lymphoproliferation in the present study (26.1%) was approximately about half the outbreak reported in the EUROclass trial (40.5%) [69]. Additionally, there was a significant difference between the hepato-splenomegaly prevalence rate in B-lymphopenic cases and patients with 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 the germinal center step, which can also explain the reduced level of B cells in the peripheral blood of these selected groups of patients. In our cohort, the prevalence rate of malignancy was 7.2% (28 cases in 387 CVID patients) which is consistent with a previous systematic review and meta-analysis that showed that 48 studies assessed malignancy and reported 790 cases of malignancies among 8123 CVID studied (9.7%) patients among which five of them had two 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]. It was reported that malignant lymphoma comprises 3.37% of all malignancies worldwide [72,73]. In contrast, current study results indicated 78.5% of all malignancies (22 cases in 28 malignant patients) in CVID patients belong to lymphoma, which was equal in the B-lymphopenic individuals (11 cases) and patients with normal B cell count (11 cases). In contrast, another study reported a 40.5% lymphoma prevalence rate in sporadic CVID patients with mostly adult-onset [74]. Although over the recent years, the early recognition and medical treatment of CVID have ameliorated, there are several records from epidemiological findings showing a high frequency of malignancy in these cases leads to the high occurrence of death [75,76]. In this regard, the mortality rate among patients with malignancy was high (40.7%) in the present study. Up to now the exact pathological mechanisms for this high outbreak of malignancy expansion are not fully specified; however, various mechanisms including impaired clearance of oncogenic viruses, genetic

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predisposition, immune dysregulation, impaired genetic stability, and iatrogenic causes have been mentioned to contribute to the development of malignancies in CVID cases [74], however, our study suggested that this is independent of B-cell lymphopenia.

The gut has been considered as the largest lymphoid organ which contains the major proportion of lymphocytes. These mentioned lymphocytes along with other immune cells, including macrophages and dendritic cells manage the mucosal immune system's balance which is in close contact with microorganisms' antigens such as viruses, bacteria, and parasites. Any related dysfunctions regarding the regulatory mechanisms might result in inflammation and GI diseases. Therefore, in IEI patients with cellular or humoral immunity dysfunction, observing GI complications is not beyond expectation. It has been reported that 5-50% of IEI patients are diagnosed with a degree of GI complications [77]. Various clinical immunologists have reported a high incidence of GI presentations in patients diagnosed with CVID ranging from 20-60%. Most of the patients have transient or chronic diarrhea, and some of them are also diagnosed with malabsorption and weight loss [78]. Following previous data [79-82], GI complications in our study were about 58.9%, which was slightly higher among patients with B cells lymphopenia. Some CVID patients might be diagnosed with inflammatory and/or autoimmune GI 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 GI complications is 2.8 times higher compared to patients without these complications [83]. In accordance with this statement, 3.6% of patients in our study died due to various types of GI complications. CVID-related enteropathy has various characteristics, including the absence of plasma cells, follicular lymphoid hyperplasia, prominent intraepithelial lymphocytosis, and villous blunting. Besides, Ig replacement therapy cannot ameliorate enteropathy presentations. This might be an explanation for why the rate of GI complications is still high despite regular Ig therapy [84].

Ig replacement therapy and long-acting antibiotics are usually prescribed for CVID patients at particular intervals during their lifetime. Although these mentioned treatments reduced the episodes of infections and increased the survival rate among these patients, it seems that it does not have any protective effect on some non-infectious complications, including autoimmunity, malignancies, structural and functional lung disease, and GI presentations. These complications should be considered important since the inflammatory and autoimmune conditions might increase the mortality and morbidity rate. The mortality rate in our study was reported as about 24.5%. In line with previous studies, respiratory complications and lung failure were the most cause 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 among different studies. In a recent study by Ho et al., the rate of bronchiectasis was reported among 32.3% of patients [7]. In another study conducted by Busse et al., 42% of CVID patients

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who had recurrent pneumonia were diagnosed with bronchiectasis [85]. It should also be noted that, although most of the patients are under Ig therapy, some CVID patients still develop bronchiectasis. According to various studies, bronchiectasis might be the consequence of decreased switch memory B cells and deteriorated antibody production [86]. This might clarify why bronchiectasis is significantly higher among patients with B cell lymphopenia rather compared to patients with normal B cells. Furthermore, various malignancies, especially lymphoma, are among the main culprits which increase the mortality rate in patients diagnosed with CVID [83]. In our study, seven patients lost their lives due to cancers, and malignancy was the second most common reason for death.

Due to the cultural diversity in different regions of the world, some determining factors such as the consanguinity rate are different. In this regard, a higher rate of certain inheritance patterns like autosomal disease can be predicted. Moreover, the different genetic backgrounds of the studied CVID cohort may be dependent on founder mutation 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, which can lead to a reduction in the age of diagnostic delay and proper management without developing complications. All these parameters should be considered regarding the generalization of the findings of this study and therefore B cell lymphopenia should be further studied in other CVID cohorts worldwide in the future. One of our limitations in the current study was the lack of genetic diagnosis. The evaluation of genetic findings may open up the possibility of evaluation of B cell lymphopenia with normal B cells patients and potentially can suggest targeted treatment for a selected group of patients in future studies.

Conclusion

In CVID patients, not only B-cell defects but also cellular abnormalities and immune dysregulation have been detected. As a result, a broad spectrum of clinical presentations such as infectious and non-infection ones 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 rate of mortality, which is also more common in B-cell lymphopenic CVID patients and might be challenging for physicians to manage the complications. 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 on patients' quality of life. Our findings can be a prognostic guide for physicians in order to suspect CVID in patients with a history of non-infections complications. These findings in patients can lead clinicians to consider CVID and request additional tests for better diagnosis. This notion may lead to a reduction in the age of delay diagnosis and subsequently, prevent to change clinical manifestations to severe types and helps to better therapeutic approaches.

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Table 1. Demographic data of the 387 CVID patients With B lymphopenia and normal B cells.

Parameters	All CVID patients (n=387)	CVID with B lymphopenia (n=168)	CVID with normal B cells (n=219)	*p*-value
Sex ratio (M/F)	222/165	98/70	124/95	0.73
Consanguinity; N (%)	215 (55.6%)	102 (60.7%)	113 (51.6%)	0.07
Family history of IEI; N (%)	47 (12.1%)	19 (11.3%)	28 (12.8%)	0.65
Age of patients at the time study; Median years (range)	25.0 (14.0-35.0)	27 (18.0-38.0)	22 (12.2-32.7)	0.02*
Age at onset of symptoms; Median years (range)	12.0 (0.5-8.0)	2.0 (0.5-9.0)	2.0 (0.5-8.0)	0.89
Age at the time of diagnosis; Median years (range)	10.0 (3.0-21.0)	10.0 (4.0-26.2)	9.0 (2.6-19.0)	0.13
Dead/Alive	82/252	42/103	40/149	0.10

M, Male; F, Female; N, Count; Y, Year.
The median is shown [with 25th and 75th percentiles].
** p-value is statistically significant <0.05*

Table 2. Immunologic profile and laboratory data comparison between CVID patients With B lymphopenia and normal B cells.

Laboratory finding	All CVID patients (n=387)	CVID with B lymphopenia (n=168)	CVID with normal B cells (n=219)	*p*-value
IgG; mg/dL (IQR)	220 (50-470)	198.0 (29.5-493.0)	229.5 (71.2-440.5)	0.40
IgA; mg/dL (IQR)	9.5 (1.8-37.0)	9.0 (0.7-36.0)	10.5 (2.0-40.0)	0.17
IgM; mg/dL (IQR)	25.0 (8.5-50)	24.0 (8.0-53.0)	25.0 (9.0-50.5)	0.96
Neutrophils; % (IQR)	54.0 (41.0-67.0)	57.0 (44.0-68.0)	53.0 (37.2-65.0)	0.03*
Neutrophils; cells/ µL (IQR)	3848.0 (2475.0-6014.0)	3914.3 (2377.0-6545.3)	3776.0 (2720.0-5636.4)	0.83
Lymphocyte; % (IQR)	35.0 (24.3-50.0)	30.5 (21.0-46.0)	38.0 (27.0-52.0)	0.002*
Lymphocyte; cells/µL (IQR)	2498.4 (1704.0-4221.5)	2224.8 (1555.0-3503.2)	2717.2 (1907.5-4694.0)	0.003*
CD3+ T cell; % (IQR)	74.0 (64.0-83.0)	82.0 (71.0-88.0)	69.0 (60.0-77.0)	<0.001*
CD3+ T cell; cells/µL (IQR)	1778.4 (1244.8-2998.3)	1632.3 (930.0-2839.0)	1971.8 (1299-3073.6)	0.04*
CD4+ T cell; % (IQR)	32.0 (23.0-42.0)	32.0 (19.0-44.0)	33.5 (25.0-42.0)	0.18
CD4+ T cell; cells/µL (IQR)	771.8 (433.7-1349.0)	626.5 (339.7-1101.2)	954.6 (600.7-1647.7)	<0.001*
CD8+ T cell; % (IQR)	35.0 (25.0-50.0)	41.0 (31.0-56.0)	30.0 (22.2-42.0)	<0.001*
CD8+ T cell; cells/µL (IQR)	889.4 (549.9-1425.2)	890.8 (483.6-1567.2)	888.0 (564.8-1317.0)	0.95
CD19 lymphocyte, % (IQR)	9.0 (4.0-17.0)	4.0 (2.0-6.0)	16.0 (11.5-23.0)	<0.001*
CD19 lymphocyte; cells/µL (IQR)	210.9 (79.3-493.6)	73.4 (36.1-144.0)	445.7 (258.8-915.8)	<0.001*
CD16 lymphocyte, % (IQR)	7.0 (5.0-11.0)	7.0 (4.0-10.4)	7.4 (5.0-12.0)	0.54
CD16 lymphocyte; cells/µL (IQR)	182.2 (105.4-345.3)	154.4 (64.4-292.4)	217.8(140.0-418.7)	0.02*
CD21 lymphocyte, % (IQR)	4.7 (2.07-8.7)	2.9 (0.4-6.5)	5.7(2.1-12.7)	0.08
CD21 lymphocyte; cells/µL (IQR)	3.6 (0.7-9.8)	1.05 (0.1-4.6)	7.6(2.1-12.8)	0.03*

Normal range listed is for adult; IQR, Range with 75th percentile and 25th percentiles; N, Count. Ig; Immunoglobulin

The median is shown [with 25th and 75th percentiles].

** p-value is statistically significant <0.05*

Table 3. Clinical phenotypes comparison between CVID patients With B lymphopenia and normal B cells.

Parameters	All CVID patients (n=387)	CVID with B lymphopenia (n=168)	CVID with normal B cells (n=219)	*p*-value
Infection only	130 (33.6)	44 (26.2)	86 (39.3)	<0.001*
Non-infectious complications	257 (66.4)	124 (73.8)	133 (60.7)	<0.001*
Autoimmunity	94 (24.3)	53 (31.5)	41 (18.7)	0.003*
Lymphoproliferation	83 (21.4)	39 (23.2)	44(20.1)	0.45
Enteropathy	136 (35.1)	61 (36.3)	75 (34.2)	0.67
Allergy	73 (18.9)	39 (23.2)	34 (15.5)	0.05
Malignancy	28 (7.2)	14 (8.3)	13 (5.9)	0.35

n; Number

** p-value is statistically significant <0.05*

Table 4. Specific organ involvement between CVID patients With B lymphopenia and normal B cells.

Parameters	All CVID patients (n=387)	CVID with B lymphopenia (n=168)	CVID with normal B cells (n=219)	*p*-value
Cardiovascular complications	32 (8.3%)	19 (11.3%)	13 (5.9%)	0.05
Hematologic complications	72 (18.6%)	42 (25%)	30 (13.7%)	0.004*
Musculoskeletal complications	29 (7.5%)	18 (10.7%)	11 (5%)	0.03*
Neurologic complications	71 (18.3%)	31 (18.5%)	40 (18.3%)	0.96
Dermatologic complications	119 (30.7%)	66 (39.3%)	53 (24.2%)	0.001*
Endocrine complications	31 (8.0%)	19 (11.3%)	12 (5.5%)	0.03*
Non-infections gastrointestinal complications	228 (58.9%)	100 (59.5%)	128 (58.4%)	0.83
Rheumatoid complications	67 (17.3%)	34 (20.2%)	33 (15.1%)	0.18
Multiple sites complications	259 (67%)	120 (71.4%)	139 (63.5%)	0.09

n; Number

** p-value is statistically significant <0.05*

Figure 1. Age distribution of different non-infectious complications among CVID patients With B lymphopenia and normal B cells.

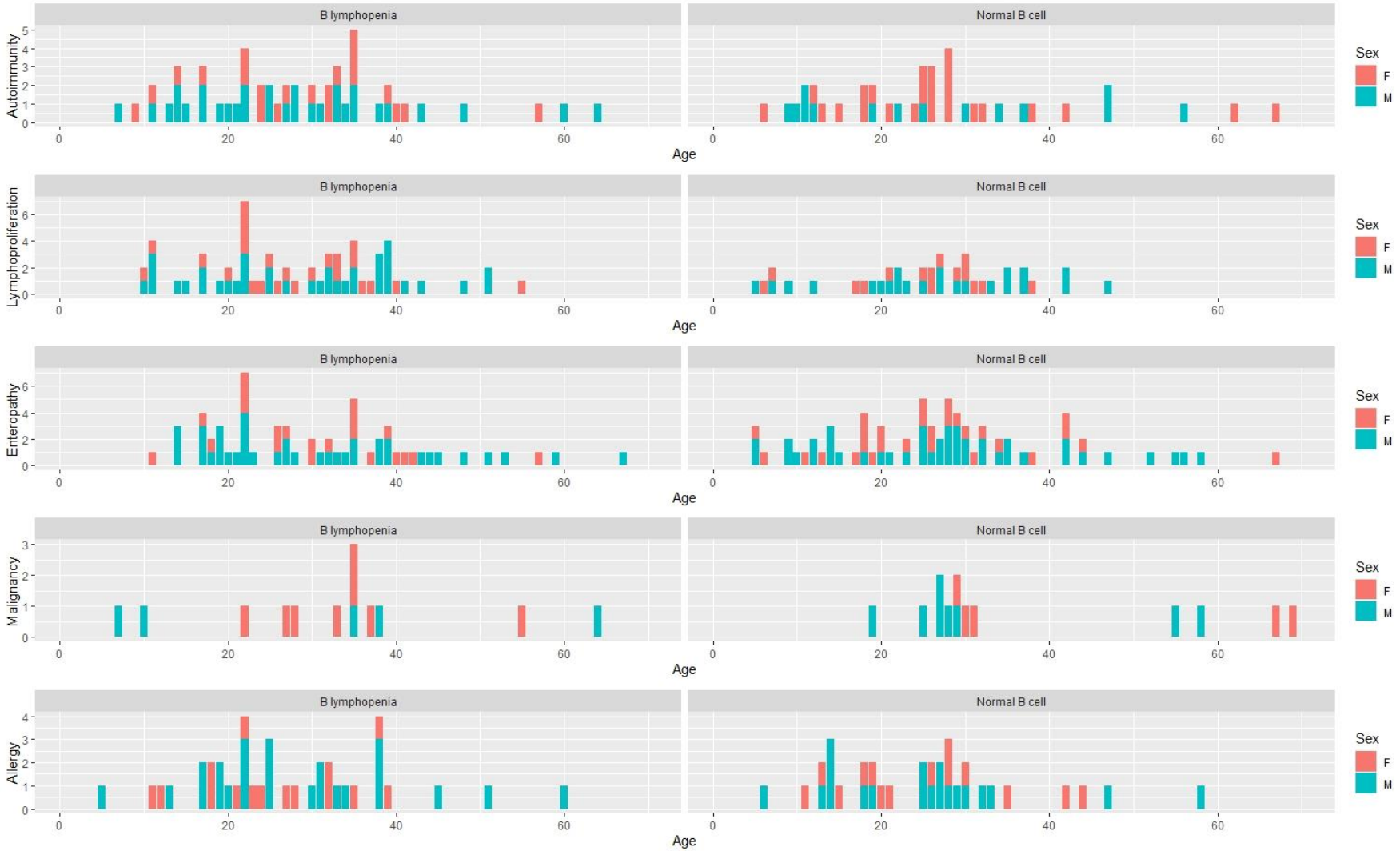
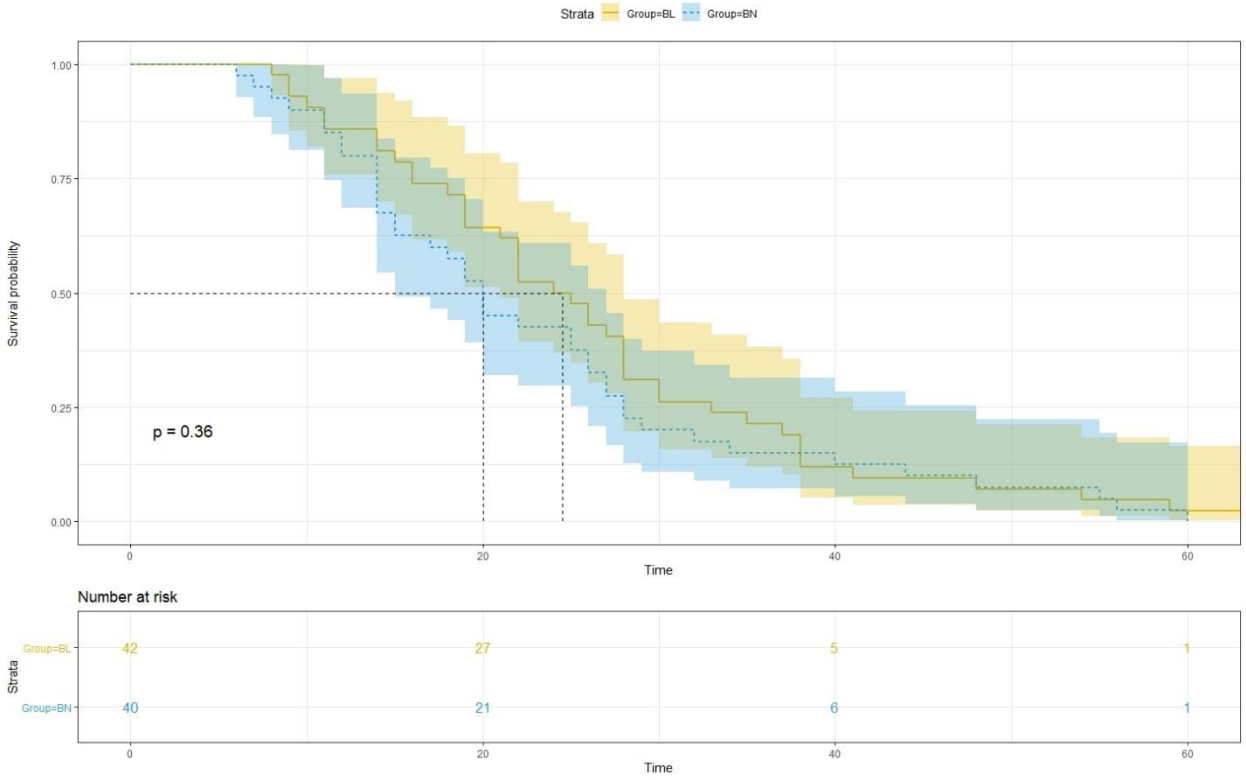


Figure 2. Kaplan-Meier graph depicting patient survival between CVID patients with B cell lymphopenia (BL) and with normal B cell counts (BN).



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