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Bronchiectasis in Patients with the Common Variable Immunodeficiency (CVID)

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Abstract

Background/objectives: The common variable immunodeficiency (CVID) is known as the most prevalent symptomatic primary immune deficiency (PID) diseases, which is characterized by lower antibody serum levels as well as several infectious and noninfectious manifestations. In this regard, Bronchiectasis is considered as a common respiratory complication and a vital challenge in CVID cases. This study aimed to evaluate the prevalence of bronchiectasis and investigate its association with other manifestations in CVID patients.

Methods: A total of 297 patients diagnosed with CVID according to the relevant criteria were included in the current study. The query was performed to collect the participants' demographic data, clinical manifestations, and laboratory findings. The analysis was performed between the two groups of the study including CVID patients with bronchiectasis and those without it.

Results: Overall, the prevalence rate of bronchiectasis was calculated to be 28.3%. Also, CVID patients with bronchiectasis had significant higher prevalence rates of respiratory manifestations, recurrent infections, otitis, clubbing, lymphoproliferative diseases, urinary tract infections, gastrointestinal diseases, dermatologic infections, allergy, and autoimmunity compared to the group including the patients without bronchiectasis. Notably, no significant differences were observed in antibodies serum levels between the patients with and without bronchiectasis. Moreover, CD19+ lymphocytes and CD8+ lymphocytes had significantly lower and higher percentages in CVID patients with bronchiectasis compared to those without it, respectively.

Conclusion: The higher prevalence of bronchiectasis in CVID patients might be correlated with some other severe respiratory and off-respiratory clinical complications. Therefore, these manifestations should be precisely managed to impede a serious condition of bronchiectasis in CVID patients.

Keywords: Common variable immunodeficiency, bronchiectasis, clinical manifestations.

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Introduction

Common variable immunodeficiency (CVID) is a heterogeneous group of primary immune deficiency (PID) diseases, which is characterized by diminished IgG, IgA, and/or IgM serum levels as well as poor antibody responses to both protein and polysaccharide antigens (1). Clinically, this disease is recognized as the most frequent PID with a prevalence of 1:50,000–1:20,000. Also, most of the patients diagnosed with CVID are in age range of 25 to 45 years old. It is noteworthy that men and women were shown to be equally affected (2). Defect in B cell differentiation is a crucial issue in these patients, as mutation in genes has been recognized to be associated with activation, proliferation, and differentiation of B cells in them (3). However, many underlying defects are undetected yet.

CVID Patients manifest various clinical manifestations such as recurrent infections, enteropathy, autoimmunity, interstitial lung disease, lymphoproliferation, malignancy, and allergic diseases (4). Among different clinical manifestations of CVID patients, respiratory tract complications (especially refractory sinusitis, otitis media, bronchitis, pneumonia, and bronchiectasis) are considered as the most frequent ones. In addition, *Streptococcus pneumoniae* and *Haemophilus influenza* are the most common bacterial pathogens affecting the respiratory tract in these patients (5).

Delay in diagnosis and following that, a poor management of respiratory disorders would lead to the presentation of irreversible pulmonary complications including bronchiectasis. In this regard, it has been indicated that only some of the affected CVID patients present bronchiectasis (6). Moreover, it has been demonstrated that the majority of CVID patients are suffering from at least 1 obvious bacterial lower respiratory tract infections (RTI) and bronchiectasis (7, 8). Bronchiectasis is determined as a chronic airway disease presented by atypical bronchial and bronchiolar dilatation (9, 10). Bronchiectasis destroys the airways and the parenchyma of lungs by means of the frequent infections and inflammation, which are known as the reasons of a reduction in the lungs' function (10, 11).

In the present study, we aimed to evaluate bronchiectasis in patients with CVID as well as investigating different demographic data, clinical manifestations, and immunological characteristics in patients with and without bronchiectasis.

Materials and methods

Study population

A total of 297 patients who were referred to Children's Medical Center (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran) were included in the present study. CVID patients were diagnosed based on the updated ESD/PAGID criteria including considerably reduced IgG levels (at least 2 SD under the mean of the patients' age), a considerable reduction in IgM and or IgA levels, lack of isohemagglutinins and/or inadequate response to vaccines, excluding other hypogammaglobulinemia in those individuals with age >4 years old, and no evidence of any significant T-cell deficiency. Written informed consents were also obtained from all the participants included.

Methods

A query was perfomed to collect the following data: (i) demographic data such as the onset age, the diagnosis age, delay in diagnosis, and consanguinity; (ii) clinical presentations including pulmonary infections, gastrointestinal complications, allergy, enteropathy, lymphoproliferative disorder, presence of autoimmune diseases, and malignancy; and (iii) lab findings such as IgG, IgM, and IgA serum concentrations, complete blood count (CBC) , differentiation, and lymphocyte subsets evaluations. Thereafter, demographic features, clinical manifestations, and laboratory data were compared in the two groups of this study as folllows: (i) CVID-affected patients with bronchiectasis and (ii) those without bronchiectasis. A clinical immunologist supervised the entire diagnosis method.

Statistical analysis

The obtained data were analyzed using SPSS 16.0 software (Chicago, USA). By the use of Kolmogorov---Smirnov and Shapiro---Wilk tests, we estimated whether data were parametric or nonparametric values. Quantitative variables were also analyzed by Mann-Whitney U and Kruskal- Wallis H tests. The statistical significance level was considered as $P < .05$.

Results

Characteristics of Patients

297 CVID patients (128 men and 169 women) with a median age of 24 years old were included in this study. The median current age and onset of the participants were 24 and 108 months, respectively. Also, the consanguinity was noted in 162 CVID patients (54.7%). Accordingly, other demographic data are provided in **Table 1**.

Among the patients with bronchiectasis included in this study, 47 (56%) cases were men and 37 (44%) subjects were women ($p = 0.836$). The analysis revealed that the median age of the patients at the onset of diagnosis was 156 months for the patients with bronchiectasis and 90 months for the patients without bronchiectasis, and this difference was statistically significant ($p = 0.000$). out of the included patiens, 42 patients with consanguinity showed bronchiectsis. Moreover, 32 subjects out of all CVID patients were recognized to have a family history, and among them, 9 cases were diagnosed with bronchiectasis, and 23 cases had no bronchiectasis ($p = 0.371$). Also, the patients included in the present study were followed-up for a median duration of 13 months. During the period of the investigation, out of all CVID-detected patients 56 cases died in which 15 cases were identified to have bronchiectasis. **Table 1** illustrates the epitome of the demographic data of all CVID patients.

Clinical Manifestations

Overall, CVID-affected patients represented several clinical manifestations. The major proportion of these presented clinical manifestations was found to be related to respiratory tract disorders. Correspondingly, 76 cases (28.3%) were shown to have upper respiratory tract (URT) infections and 72 cases (26.8%) showed lower respiratory tract (LRT) infection. In addition, Diarrhea (n = 54), non-respiratory infections (n = 39), fever (n = 9), failure to thrive (FTT) (n = 8), organomegaly (n = 5), arthritis (n = 3), and autoimmunity (n = 3) were the other manifestations. Our survey showed that 84 patients (28.3%) manifested bronchiectasis, while 213 cases (71.7%) had no bronchiectasis. Notably, 59.3% of the patients included in this study simultaneously presented bronchiectasis and respiratory tract disorders.

Table 1. Demographic data of the CVID patients with and without bronchiectasis

Parameters	Total patients	Bronchiectasis +	Bronchiectasis -	*p*-value
Age at the study time, m (IQR)	288 (180-384)	330 (252-444)	258 (168-360)	0.000
Age at the diagnosis time , m (IQR)	108 (36-234)	156 (96-315)	90 (24-204)	0.000
Delay diagnosis, m (IQR)	48 (12-107)	84 (32-142)	36 (12-84)	0.000
Course of disease, m (IQR)	192 (60-288)	252 (168-333)	144 (21-262)	0.000
Follow-up, m (IQR)	13 (6-18)	16 (7-19)	9.2 (1.7-13.7)	
Gender, N (%)				
Male	169 (56.9%)	47 (56%)	122 (57.3%)	
Female	128 (43.1%)	37 (44%)	91 (52.7%)	
Consanguinity, N (%)	162 (54.7%)	42 (50.6%)	120 (56.3%)	0.373
Family history, N (%)	32 (16.2%)	9 (13%)	23 (18%)	0.371
Mortality status, N (%)				0.318
Alive	202 (68%)	54 (64.3%)	148 (69.5%)	
Dead	56 (18.9%)	15 (17.9%)	41 (19.2%)	
Unknown	39 (13.1%)	15	24	

Note. For quantities data, the median is shown [with IQR, 25th, and 75th percentiles]. N, Count. *p-value <0.05 has been considered as statistically significant.

Table 2. Clinical manifestations and organ involvement of the CVID patients with and without bronchiectasis

Parameters	Total patients	Bronchiectasis +	Bronchiectasis -	p-value
Recurrent infections, N (%)	174 (58.6%)	62 (73.8%)	112 (52.6%)	0.001
Otitis, N (%)	143 (48.1%)	52 (61.9%)	91 (42.7%)	0.003
Pneumonia, N (%)	206 (69.4%)	71 (84.5%)	135 (63.4%)	0.000
Sinusitis, N (%)	148 (49.8%)	62 (73.8%)	86 (40.4%)	0.000
Bronchiectasis, N (%)	84 (28.3%)	-	-	
Clubbing, N (%)	70 (23.6%)	39 (46.4%)	31 (14.6%)	0.000
Autoimmunity, N (%)	79 (26.6%)	32 (38.1%)	47 (22.1%)	0.005
LPD, N (%)	81 (27.3%)	36 (42.9%)	45 (21.1%)	0.000
Oral ulcer, N (%)	45 (15.2%)	10 (12%)	35 (16.4%)	0.345
Chronic diarrhea, N (%)	116 (39.1%)	48 (57.1%)	68 (31.9%)	0.000
Allergy, N (%)	63 (21.2%)	27 (32.1%)	36 (16.9%)	0.004
Malignancy, N (%)	14 (4.7%)	3 (3.65%)	11 (5.2%)	0.560
FTT, N (%)	71 (23.9%)	33 (39.3%)	38 (17.8%)	0.000
Conjunctivitis, N (%)	40 (13.5%)	22 (26.2%)	18 (8.5%)	0.000
Tooth decay, N (%)	10 (3.4%)	4 (4.8%)	6 (2.8%)	0.403
Candidiasis, N (%)	49 (16.5%)	10 (11.9%)	39 (18.3%)	0.180
Meningitis, N (%)	8 (2.7%)	3 (3.6%)	5 (2.4%)	0.566
Respiratory tract infections, N (%)	247 (83.2%)	80 (95.2%)	167 (78.4%)	0.000
Eyes disorders, N (%)	13 (14.4%)	9 (39.1%)	4 (6%)	0.000
Urinary tract infections, N (%)	47 (39.5%)	20 (60.6%)	27 (31.4%)	0.004
Heart problems, N (%)	31 (27.7%)	11 (36.7%)	20 (24.4%)	0.198
Hematological diseases, N (%)	67 (50.8%)	22 (59.5%)	45 (47.4%)	0.212
Anemia, N (%)	47 (15.8%)	15 (17.9%)	32 (15%)	0.500
Neutropenia, N (%)	17 (17.9%)	6 (25%)	11 (15.5%)	0.294
Thrombocytopenia, N (%)	25 (25.3%)	9 (34.6%)	16 (21.9%)	0.201
Leukopenia, N (%)	12 (14.1%)	5 (21.7%)	7 (11.3%)	0.219
Pancytopenia, N (%)	18 (20.5%)	4 (19%)	14 (20.9%)	0.855
Gastrointestinal diseases, N (%)	212 (75.5%)	71 (86.6%)	141 (70.5%)	0.005
Rheumatoid, N (%)	62 (45.3%)	26 (63.4%)	36 (37.5%)	0.005
Musculoskeletal disorders, N (%)	23 (21.3%)	9 (33.3%)	14 (17.3%)	0.078
Neurological disorders, N (%)	67 (47.5%)	23 (60.5%)	44 (42.7%)	0.060
Dermatologic infections, N (%)	112(64%)	40 (78.4%)	72 (58.1%)	0.011
Endocrine disorders, N (%)	25 (9.6%)	9 (11.5%)	16 (8.7%)	0.482
Multiple sites, N (%)	243(87.7%)	79 (100%)	164 (82.8%)	0.000

Abbreviations: LPD: Lymphoproliferative disorder; FTT: Failure to thrive. Note. For quantities data, the median is shown [with IQR, 25th, and 75th percentiles]. N, Count. *p-value <0.05 has been considered as statistically significant.

During the follow-up period, several clinical manifestations such as RTI (95.2%), gastrointestinal disorders (86.6%), recurrent infections (73.8%), pneumonia (84.5%), dermatologic infections (78.4%), and sinusitis (73.8%) were recorded from the CVID patients with bronchiectasis. Out of 247 patients with RTI, 80 cases were diagnosed with bronchiectasis. Also, out of 174 patients with recurrent infections, 62 cases had bronchiectasis compared with 112 subjects who had not bronchiectasis ($p = 0.001$). Similarly, among 206 cases who showed pneumonia, 135 had not bronchiectasis while 71 others manifested bronchiectasis ($p = 0.001$). Accordingly, these data reveal that the rates of respiratory disorders were significantly higher in the patients with bronchiectasis compared to the

patients who had not bronchiectasis. Regarding the other clinical manifestations of the participants of this study, otitis (p = 0.003), sinusitis (p = 0.000), clubbing (p = 0.000), autoimmunity (p = 0.005), lymphoproliferative disorders (p = 0.000), chronic diarrhea (p = 0.000), allergy (p = 0.004), FTT (p = 0.000), conjunctivitis (p = 0.000), eyes problems (p = 0.000), urinary tract infections (p = 0.004), Gastrointestinal diseases (p = 0.005), rheumatoid (p = 0.005), dermatologic infections (p = 0.011), and multiple sites disorders (p = 0.000) were significant between the two groups including the patients with and without bronchiectasis. The details of these clinical manifestations are categorized in **Table 2**.

Immunological Findings

The analysis showed that the patients with bronchiectasis had a significantly lower frequency of lymphocytes compared to those patients without bronchiectasis (29% vs. 38 %; p = 0.000). However, the frequency of neutrophils was significantly higher in the group of the patients with bronchiectasis in comparison with another group (65 vs. 52 %; p = 0.000). Immunological assay of lymphocytes demonstrated that $CD3^+$ cells were not expressed significantly in the patients with bronchiectasis compared to the patients without bronchiectasis (p = 0.075 and 0.591, respectively). In contrast, the expression of $CD8^+$ cells was significantly higher in the group of the patients with bronchiectasis compared to the other group (p = 0.000). However, other investigated lymphocytes including $CD4^+$, $CD56^+$, $CD16^+$, $CD19^+$, and $CD20^+$ cells had an equal median of percentage in both groups. Among them, only the difference in the median of $CD19^+$ cells was significant (p = 0.009). In the investigation of the serum levels of antibodies, it was demonstrated that IgG and IgE had lower medians of serum levels in the patients with bronchiectasis compared to the patients without bronchiectasis (p = 0.488 and 0.108, respectively). Also, the median serum levels of IgA were identical between the two studied groups (p = 0.726). In contrast, IgM exhibited a slightly higher median of serum levels in the patients with bronchiectasis compared to the other group (p = 0.338).

Table 3. Laboratory data of the CVID patients with and without bronchiectasis

Parameters	Total patients (n = 297)	Bronchiectasis +	Bronchiectasis -	p-value
WBC, cell/µl (IQR)	7900 (5510-11000)	8300 (5645-11875)	7855 (5400-10475)	0.399
Lymphocyte, % of total WBC (IQR)	35 (24-50)	29 (20-37)	38 (27-52)	0.000
Neutrophils, % of total WBC (IQR)	55 (41-67)	65 (54-72)	52 (36-63)	0.000
Platelet, cell/µl (IQR)	232500 (118250-321750)	186000 (82000-328000)	240000 (137000-318000)	0.143
Hb, g/dl (IQR)	12 (11-13)	12 (11-13)	12 (11-13)	0.549
CD3, % of lymphocytes	74 (63-83)	76.9 (66.5-84)	73 (61.7-82)	0.075
CD4, % of lymphocytes	32 (23-42)	30.2 (19.7-39.2)	35 (23-42)	0.059
CD8, % of lymphocytes	35 (25-50)	45 (31-57)	34 (23-45)	0.000
CD56, % of lymphocytes	6 (3-9)	6 (5-9)	6 (3-10)	0.516
CD16, % of lymphocytes	7 (5-11)	7 (5-10)	7 (5-12)	0.734
CD1656, % of lymphocytes	5 (3-7)	5.5 (3.7-8.2)	5 (2.7-7.2)	0.591
CD19, % of lymphocytes	9 (4-17)	6.5 (3.2-12.7)	11 (4-20)	0.009
CD20, % of lymphocytes	11 (4-20)	10 (3-15)	11 (5-22)	0.115
IgG, mg/dl (IQR)	226 (77-470)	197 (77-499)	233 (74-470)	0.488
IgA, mg/dl (IQR)	19 (7-47)	19 (7-47)	19 (6-47)	0.726
IgM, mg/dl (IQR)	28 (13-58)	32 (14-68)	26 (13-52)	0.338
IgE, mg/dl (IQR)	1 (0-5)	1 (0-3)	1.7 (0.6-5)	0.108

Abbreviations: WBC: white blood cells; Hb: Hemoglobin; Ig: Immunoglobulins; CD: Cluster of Differentiation; y: year.

Note. For quantities data, the median is shown [with IQR, 25th, and 75th percentiles]. N, Count. *p-value <0.05 has been considered as statistically significant.

Discussion

Previous studies have indicated that the onset of CVID symptoms could occur at any age from the childhood to the adulthood (8). Our results showed that the patients diagnosed with CVID with a median of 108 months, the onset was significantly higher in the patients with bronchiectasis compared to the patients without it. Also, we have exhibited that the median delay diagnosis was significantly higher in the patients with bronchiectasis compared to the other group. This diagnostic delay, which was previously reported in some studies, was more than 5 years in the developed countries (12). In a study on CVID and bronchiectasis, despite a higher median of ages at the time of diagnosis for the CVID patients who showed bronchiectasis, no significant difference was observed between the patients with and without bronchiectasis (13). In contrast to our findings, it was shown that no significant difference was presented for the median delay in diagnosis between the two studied groups (13). However, another study exhibited a significantly higher median of age at the time of diagnosis for the patients with bronchiectasis compared to those patients without bronchiectasis. They have also shown a significantly higher median of delay in diagnosis in the patients who had bronchiectasis (14).

Chronic respiratory manifestations are the most common CVID clinical features (between 30% and 60%) among the affected patients (15-17). It has been demonstrated that bronchiectasis is the most frequent cause of mortality and morbidity among CVID patients. Interestingly, the prevalence of bronchiectasis remarkably varied from 11.2% to 90% in the vast cohort studies (15). However, it has been reported that bronchiectasis might be progressive, which could be considered as the reason of mortality and morbidity in patients with CVID (13). In the current study, bronchiectasis was documented in 28.3% of the total CVID patients. In this regard, bronchiectasis has been hightly presented in ourin CVID cases (6, 18), which indicate that these patients need to receive more dosages of intravenous immunoglobulin (IVIG) compared to those CVID patients without bronchiectasis. The increased dose would consequently lead to the augmentation of the transportability of respiratory mucus and decrease the inflammation of the airways (18). Nevertheless, a cohort study conducted on CVID patients revealed that bronchiectasis has no relationship with the cause of the patient's death (14). In this study, consistent with previous studies, we indicated that respiratory complications (especially pneumonia) are the most frequent clinical manifestations (5). Similarly, another study reported that 73% of CVID patients exhibited pneumonia, which is similar to the current study result (19). Similar to our findings, Ramzi et al. in their study demonstrated that CVID patients have prevalence rates of 60.3% and 41.9% for pneumonia and sinusitis, respectively (13). However, Hampson et al. reported that interstitial lung diseases (ILD) can be known as an immune-mediated manifestation and the main reason for lung function decline, rather than recurrent infections and bronchiectasis in CVID-affected patients (20). ILD affect almost 10-20% of CVID cases; however, this rate might be higher (21, 22).

Further investigations on the clinical features of the present study have demonstrated that RTI, pneumonia, and sinusitis had a significantly higher prevalence rate in the CVID patients with bronchiectasis compared with the subjects without bronchiectasis. This is in line with another study on CVID cases in which the prevalence rates of pneumonia and RTI were significantly higher in CVID-affected patients who had bronchiectasis in comparison with those without it. Besides, the prevalence of sinusitis was remarkably higher in patients with bronchiectasis compared to those patients without bronchiectasis (13). Interestingly, it was reported that CVID patients with bronchiectasis could also have no history of pneumonia diagnosis, which may be due to subclinical immune dysregulation and intense inflammation (23).

Recurrenct infections along with autoimmune and/or inflammatory manifestations are recognized as

the two main phenotypes of CVID clinical features (2, 16). The current study represented that gastrointestinal diseases, dermatologic infections, and recurrent infections are the most common non-respiratory complications associated with CVID. Our analysis performed on CVID patients revealed that the frequencies of gastrointestinal diseases, dermatologic infections, and recurrent infections were significantly higher in the patients with bronchiectasis compared with those without it. Similarly, we demonstrated that CVID patients with bronchiectasis have significantly higher frequencies of otitis, chronic diarrhea, conjunctivitis, FTT, and clubbing compared to the patients without bronchiectasis. Accordingly, this is in line with the other study on CVID cases in which the prevalence of otitis was significantly higher in patients who had bronchiectasis (13). In contrast, although FTT and clubbing had higher prevalence rates in patients with bronchiectasis, these rates were not significant (13). Similarly, the prevalence rates of tooth decay, candidiasis, and meningitis were not significant, despite the increased rates of them in patients with bronchiectasis in the present study. Further analysis demonstrated that hematological diseases (50.8%), neurological disorders (47.5%), and rheumatoid (45.3%) had also high prevalence in CVID patients. We have also reported that the prevalence rates of autoimmunity, lymphoproliferative disorders, allergy, and rheumatoid were significantly higher in the patients with bronchiectasis compared those patients who had not bronchiectasis. It was exhibited that CVID patients are more susceptible to the developed malignancies and cancers (24). A recent study conducted on CVID showed that the prevalence of rheumatologic complications, autoimmunity, lymphadenopathy, malignancy, and asthma or allergy were not different significantly between the CVID patients with or without bronchiectasis (13). However, autoimmunity was shown to be a major manifestation with a high prevalence rate in CVID cases (19).

As discussed earlier, the characterization of CVID was studies by investigating the serum levels of antibodies and the frequencies of lymphocytes, especially B cells. We have also demonstrated that the frequency of lymphocytes was significantly lower in the patients with bronchiectasis compared with the cases without it. However, neutrophils had a significantly higher frequency in the patients with bronchiectasis compaered with the cases without it. Correspondingly, this revealed a lymphopenia profile in CVID patients with bronchiectasis. in contrast, in a study on CVID it was shown that lymphocyte had a higher median in patients with bronchiectasis compared to patients without it (13). In agreement with our results, another study demonstrated that lymphocytes had a significantly lower frequency in patients with bronchiectasis compared with patients without it. On the other hand, they have shown that neutrophils had a significantly higher frequency in patients with bronchiectasis compared with those without it (14).Our findings have demonstrated that $CD19^{+}$ lymphocytes had a significant lower proportion in the patients with bronchiectasis compared to those without it. Moreover, previous studies have indicated that patients with CVID who had bronchiectasis have a low frequency of B cells as well as low levels of IgG (25-27).

Furthermore, the possible association between CVID and bronchiectasis might be due to lower baseline IgG levels (28). A recent study performed on CVID cases showed that IgG had slightly lower serum levels in patients with bronchiectasis compared to patients without bronchiectasis (14). In contrast, a study indicated higher serum levels of IgG in CVID patients with bronchiectasis in comparison with those without it. This conflicting result might be due to the low sample size of the study and more IVIG therapies in patients with bronchiectasis compared with patients without bronchiectasis (13). In major cases of CVID, both IgG and IgA levels were shown to be either absent or dysfunctional (29). In fact, IgA plays an imperative role in the immunity of airway. Similarly, CVID patients with extremly low IgA levels had higher rates of severe respiratory infections compared with patients with higher IgA levels (12, 30).

Coclusion

The current study demonstrated that bronchiectasis is a common serious manifestation in CVID patients. Moreover, the prevalence rates of other chronic respiratory complications, infections, and autoimmunity disorders were remarkably higher in patients with bronchiectasis. Given that bronchiectasis could be considered as a major cause for higher morbidity and mortality in CVID patients, having appropriate awareness and early diagnosis are vital for improving the management and high quality of life for CVID patients.

Conflicts of interest

The author declare that he have no conflicts of interest.

Aknowledgment

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