Original Article

Important Factors Influencing Severity of Common Variable Immunodeficiency

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Abstract

Background: Common variable immunodeficiency (CVID) is a primary immune deficiency with heterogeneous complications. The purpose of this study is to determine disease severity in a cohort of CVID patients based on the suggested scoring system and investigate predisposing factors which would be helpful to predict the severity of the disease.

Methods: The study population comprised 113 CVID patients (69 males and 44 females) who were visited at Children's Medical Center (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran) during the last 30 years (from 1984–2014). According to a suggested severity scoring system, patients were divided into two groups, A and B. The clinical severity of the disease in patients was assessed with severity scores including 15 unlucky complications of the disease such as numbers of past meningitis, encephalitis or pneumonias, development of bronchopulmonary pathologies, presence of lymphoproliferative disorders, autoimmunity or malignancy.

Results: The mean serum IgG level was significantly higher in group B (308.6±195.9) compared to group A (177.8 ± 151.9; $P = 0.03$). Patients in group B had a significantly higher percentage of CD8 ($P = 0.003$). However, they had lower percentage of CD4 lymphocytes ($P = 0.08$), switched memory B cells (CD27+IgM-IgD-) ($P < 0.01$) and regulatory T cells ($P = 0.02$) than group A.

Conclusion: Using standard and universal scoring system and understanding of related factors can be applicable in clinical settings for prognosis assessment of CVID patients.

Keywords: Autoimmunity, common variable immunodeficiency, severity score

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Introduction

Common variable immunodeficiency (CVID) is the most common symptomatic primary immune deficiency (PID) characterized by marked reduction of serum IgG, IgA, and/or IgM levels. There is mainly a defect in specific antibody production against protein and polysaccharide antigens.[1] CVID leads to recurrent and chronic infections, most prevalently of the respiratory and gastrointestinal tracts. However, manifestations are not limited to infections and patients may also present with autoimmune disorders, lymphoproliferative or granulomatous diseases, and they are at greater risk for developing malignancies.[2] These non-infectious complications are evidence of dysregulation of the immune system in this clinically heterogeneous disorder. The broad clinical spectrum of CVID is not only in the type of complications, but also different patients show different severity and likely prognosis. It seems that immunoglobulin replacement, the mainstay of treatment for CVID patients, can reduce the number of bacterial infections but has no effect on autoimmune or inflammatory conditions which are the leading causes of long-term morbidity and mortality in CVID subjects.[3]

Although several investigations have been made to discover the underlying etiology of CVID, our knowledge about the basic mechanisms, more prominently of the non-infectious aspect of the disease, is still incomplete. In order to understand the disease better, several attempts have been made to classify patients based on clinical or immunologic phenotypes.[4,5] Recently, four distinct clinical phenotypes have been proposed, including no complications, autoimmune cytopenia, polyclonal lymphocytic infiltration and enteropathy, each with significantly different severity and prognosis. It is shown that the presence of clinical non-infectious complications is associated with higher mortality rate. Unexpectedly, no relation was found between serum IgG levels and survival rates. However, higher serum IgM levels were associated with increased risk of polyclonal lymphocytic infiltration and lymphoid malignancy. T-cell abnormalities were associated with a higher risk of lymphoproliferation, chronic enteropathy, and autoimmune cytopenia.[6] Diagnostic delay and inadequate treatment are two known factors which result in increased irreversible complications and mortality whereas early diagnosis and appropriate treatment can improve patient's quality of life.[7] Furthermore, parental consanguinity is an important factor in CVID and can increase the risk of early onset presentation and developing severe clinical complications due to homozygous

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mutation in comparison to compound heterozygous mutant patients.[8] Recently, Grimbacher *et al*.[9] suggested a severity scoring system for CVID patients including 15 complications of the disease such as numbers of past severe infections, development of bronchopulmonary pathologies, presence of lymphoproliferative disorders, autoimmunity or malignancy (Table 1). The aim of this study is to investigate disease severity and predisposing factors in two groups of CVID patients with mild and severe complications according to a suggested severity scoring system.[9] These data could contribute to better management and follow-up of high-risk patients who demonstrate severe complications. Moreover, knowing these data could be helpful to predict the severe condition and prognosis in early stages or at the time of diagnosis.

Materials and Methods

Patients

The present study is a retrospective cohort, as the total number of 185 patients who were diagnosed as CVID were visited at Children's Medical Center (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran).[10,11] Patients not regularly followed up were excluded from the study. Finally, a total of 113 CVID patients were enrolled in the study. The inclusion criteria for patients are defined by the European Society of Immune Deficiencies (ESID) and the Pan American Group for Immune Deficiency (PAGID) which includes reduction of at least two serum immunoglobulin isotypes (serum IgG, IgA or IgM) by two standard deviations from normal mean values for age, and exclusion of other causes of hypogammaglobulinemia in individuals aged >4 years and evidence of specific antibody deficiency.[12,13] Patients not regularly followed were excluded. Moreover, we excluded patients under 2 years of age, because of a possible diagnosis of transient hypogammaglobulinemia. The process of this study was approved by the ethics committee of Tehran University of Medical Science and all patients or their parents or legal guardians were asked to fill an informed consent.

Data collection

A 1-page questionnaire was completed for each patient to collect information such as demographic data, clinical manifestations, immunologic findings, infectious or noninfectious complications, and mortality information. The clinical severity of the disease was assessed by a suggested CVID severity score, including presence of chronic sinusitis, number of past meningitis or encephalitis, number of past pneumonias, presence of bronchiectasis or other parenchymal lung pathology, positive history of lung surgery (lobectomy or pneumonectomy), presence of granulomata, splenomegaly, or lymphadenopathy, positive history of splenectomy, coexistence of autoimmunity, lymphoma or solid tumors, presence and severity of CVID enteropathy, and rheumatologic complaints such as arthralgia.[9] All 113 patients were studied to find out the factors that influence the severity of the disease. We evaluated all patients based on the suggested severity score system and selected two groups out of the patients, namely group A which comprised 18 patients who had lower severity rating (the scores were lower than mean ± SD, total score = 1.5 ± 0.9) and group B which included 19 patients who had upper severity rating (the scores were more than mean ± SD, total score = 11.6 ± 1.9). Since the mean score for the entire patients was 6.6 ± 3.3, patients who had a score lower than 3.3 were categorized as group A and patients with scores higher than 9.6 were categorized as group B. According to the suggested severity score system, patients in group A demonstrate mild clinical complications and patients in group B manifest severe clinical complications. Patients with scores between these two groups were not entered in comparison, because we decided to compare clinical severity in patients with mild and severe complications. Then, these two selected groups were compared for probable factors influencing disease severity. The method of assessment of clinical phenotypes,[2,14,15] immunologic study[16–21] and quality of life[22] are explained in previous studies.

Statistical analysis

Statistical analysis was performed using a commercially available software package (SPSS Statistics 17.0, SPSS, Chicago, Illinois).

Table 1. Suggested CVID severity score.

Points	0	1	2	3
Chronic sinusitis	Absent	Present	—	—
Past meningitis or encephalitis	Absent	One bout	Two bouts	> Two bouts
Past pneumonia	Absent	One bout	Two bouts	> Two bouts
Bronchiectasis	Absent	One lobe	Two lobes	> Two lobes
Other parenchymal lung pathology such as fibrosis, LIP,BOOP, etc.	Absent	Suspected	—	Confirmed
Lung surgery (lobectomy or pneumonectomy)	Absent	—	—	Performed
Splenomegaly	Absent	11–14.9cm	15–20 cm	>20cm
Splenectomy	Absent			Performed
Lymphadenopathy (largest node)	Absent	<2cm	2–3 cm	>3cm
CVID enteropathy	Absent	Intermittent	Chronic but mild	Severe
Autoimmune condition	Absent	Suspected		Confirmed
Other rheumatologic complaints such as arthralgia	Absent	Suspected	Confirmed	
Granulomata	Absent	Skin only	Lung, liver or spleen	CNS(incl, eye)
Lymphoma	Absent	—	—	Present
Cancer (solid tumors) such as bowel, skin or stomach	Absent	—	—	Present

LIP = lymphocytic interstitial pneumonia; BOOP = bronchiolitis obliterans organizing pneumonia; CNS = central nervous system.

Table 2. Demographic and immunological features of patients in group A and group.

Parameters	Patients	Group A	Group B	*P*-Value
Sex (M/F)	69/44	11/7	9/10	0.405
Consanguinity (%)	61.1	50.0	63.2	0.412
Family history of PID (%)	16.8	27.8	15.8	0.376
Current age (Mean ± SD); Year	20.2 ± 12.0	18.4 ± 11.1	18.7 ± 10.4	0.914
Onset age (Mean ± SD); Year	5.9 ± 4.7	6.6 ± 9.9	3.1 ± 2.9	0.178
Age at time of diagnosis	12.7 ± 11.3	13 ± 11.8	12.3 ± 9.7	0.843
Diagnostic delay (Mean ± SD); Year	6.5 ± 6.1	6.4 ± 7.3	7.1 ± 2.8	0.716
Follow-up period (Mean ± SD); Year	6.0 ± 4.8	4.4 ± 3.7	6.6 ± 4.8	0.133
Status (Alive/Dead)	77/36	16/2	10/9	0.029*
Age at death Mean ± SD (Range); Year	17.79 ± 12.953	35 ± 15.55	17.25 ± 5.8	0.154
IgG (mg/dl)	238.3 ± 217.2	177.8 ± 151.9	308.6 ± 195.9	0.031*
IgM (mg/dl)	30.5 ± 33.9	32.6 ± 34.9	34.5 ± 29.4	0.862
IgA (mg/dl)	17.5 ± 24.8	16.5 ± 31.3	14.4 ± 15.8	0.882
CD3+ T cells (% of Lymphocytes)	75.4 ± 17.06	76.6 ± 14.4	88.1 ± 26.9	0.165
CD3+CD4+ T cells (% of Lymphocytes)	31.9 ± 12.2	37.1 ± 14.5	28.8 ± 10.6	0.082
CD3+ CD8+ T cells (% of Lymphocytes)	41.3 ± 14.5	36.1 ± 12.2	51 ± 11.9	0.003*
CD19+ B cells (% of Lymphocytes)	10.2 ± 9.1	8.4 ± 6.8	7.1 ± 4.2	0.576
Switched memory B cells	0.73 ± 0.4	1.02 ± 0.6	0.5 ± 0.2	<0.01*
Regulatory T cells	1.77 ± 0.71	2.17 ± 1.63	1.59 ± 0.42	0.022*

M = male; F = female; mg/dL = milligram/deciliter; SD = standard deviation.
Group A: 18 patients who had lower severity rating (the scores were lower than mean ± SD).
Group B: 19 patients who had upper severity rating (the scores were more than mean ± SD).
* *P* value significant at the level <0.05

The Kolmogorov-Smirnov test was performed to evaluate the normality of distribution. Parametric and non-parametric analyses were performed based on the findings of this evaluation. A *P*-value of less than 0.05 was considered statistically significant. Immunological data and CD markers were evaluated using the results of the initial test performed at diagnosis. T-test was used for statistical comparison between two groups. Linear regression was applied to determine the association between quantitative variables. Complication rates in group A versus group B were assessed using Fisher exact test. We used the Kaplan-Meier method to compare survival between the two groups through lifetime.

Results

Demographic profile

A total of 113 CVID patients including 69 males and 44 females were enrolled in the study. At the end of the study period, the mean (SD) age of the patients was 20.2 (12.0) years. The mean (SD) age at the time of disease onset and the mean (SD) age at the time of diagnosis were 5.9 (4.7) years and 12.7 (11.3) years, respectively. The mean (SD) diagnostic delay was 6.5 (6.1) years.

The patients were followed for a total of 664 patient-years with a mean (SD) follow-up time of 6.0 (4.8) years per patient. Sixty-nine patients (61.1%) were born as a result of consanguineous marriage and 19 (16.8%) cases had a positive family history of PID. More members of the family suffered from CVID, while the rest of them had selective IgA deficiency. Ninety percent of the patients had a single phenotype and the most common phenotype was infections-only (45%), followed by polyclonal lymphocytic infiltration (35%). Serum immunoglobulin levels and immunophenotyping of peripheral blood lymphocytes are summarized in Table 2.

Clinical severity and quality of life

The mean (SD) clinical severity score of CVID in this study group was 6.6 (3.3) ranging from 0 to 16. The assessed clinical severity in groups A and B was equal to 1.5 ± 0.9 and 11.6 ± 1.9, respectively. Details regarding the clinical features of all patients and also group A versus group B, used for point scoring, are provided in Tables 2 and 3. Although the patients in group B had higher probability to be the result of consanguineous marriages (63.2%), compared to group A (50.0%), this association was not significant ($P = 0.4$). The onset age in group B was not significantly lower than group A.

From all patients in group B, 17 (89.4%) suffered from overlapping clinical phenotypes, while all 18 cases (100%) in group A only experienced infectious only phenotype. Autoimmunity was rather higher in group B ($P = 0.006$) as only one suspicious condition was considered for only one patient in group A , whilst 31.6% of patients in group B already suffered from autoimmune complications of CVID. Only patients with more severe disease had autoimmune cytopenia ($P = 0.01$) and rheumatologic complaints ($P = 0.002$).

Comparison of quality of life between two groups using SF-36 questionnaire showed that group B expressed significantly reduced scores in physical (58.3 ± 21.3 vs. 65.9 ± 14.7, $P < 0.01$) and mental components (54.0 ± 19.6 vs. 62.8 ± 17.0, $P < 0.01$).

Immunologic studies

Surprisingly, the mean serum IgG level was significantly higher in group B (308.6 ± 195.9) compared to group A (177.8 ± 151.9; $P = 0.031$) (Figure 1). It seems that the difference of IgG between two groups is not the result of individual variation. Baseline IgG of all 113 patients correlated with IgA, IgM, IgE, and switched B cell. Pearson Correlation coefficients of IgG with IgA, IgM, IgE, and switched B cell were 0.197, 0.197, -0.097, and 0.365,

Table 3. Severity of CVID and Selected Complications, comparison of group A versus group.

Parameters	Total (%)	Group A (%)	Group B (%)	*P*-value
Total Score	6.6±3.3	1.5±0.9	11.6±1.9	<0.001*
Chronic sinusitis				0.325
Absent	35 (31)	9(50)	6(31.6)	
Present	78 (69)	9(50)	13(68.4)	
Past meningitis or encephalitis				0.065
Absent	101 (89.4)	18(100)	14(73.7)	
One bout	10 (8.8)	0(0)	4(21.1)	
Two bouts	1 (0.9)	0(0)	0(0)	
>two bouts	1 (0.9)	0(0)	1(5.3)	
Past Pneumonia				<0.001*
Absent	19 (16.8)	8(44.4)	0(0)	
One bout	24 (21.2)	8(44.4)	1(5.3)	
Two bouts	11 (9.7)	2(11.1)	1(5.3)	
>two bouts	59 (52.2)	0(0)	17(89.5)	
Bronchiectasis				0.002*
Absent	71 (62.8)	18(100)	8(42.1)	
One lobe	23 (20.4)	0(0)	3(15.8)	
Two lobes	9 (8)	0(0)	3(15.8)	
Other parenchymal lung pathology				0.065
Absent	97 (85.8)	18(100)	14(73.7)	
Suspected	11 (9.7)	0(0)	1(5.3)	
Confirmed	5 (4.4)	0(0)	4(21.1)	
Lung Surgery (lobectomy or pneumonectomy)				1.0
Absent	111 (98.2)	18(100)	18(94.7)	
Performed	2 (1.8)	0(0)	1(5.3)	
Splenomegaly				0.002*
Absent	65 (57.5)	16(88.9)	5(26.3)	
11–14.9 cm	40 (35.4)	2(11.1)	10(52.6)	
15–20 cm	5 (4.4)	0(0)	2(10.5)	
>20cm	3 (2.7)	0(0)	2(10.5)	
Splenectomy**				1.0
Absent	110 (97.3)	18(100)	18(94.7)	
Performed	3 (2.7)	0(0)	1(5.3)	
Lymphadenopathy (Largest Node)				0.131
Absent	72 (63.7)	17(94.4)	12(63.2)	
<2 cm	33 (29.2)	1(5.6)	4(21.1)	
2–3 cm	6 (5.3)	0(0)	2(10.5)	
>3cm	2 (1.8)	0(0)	1(5.3)	
CVID enteropathy				0.227
Absent	83 (73.5)	14(77.8)	11(57.9)	
Intermittent	12 (10.6)	3(16.7)	3(15.8)	
Chronic but mild	8 (7.1)	1(5.6)	1(5.3)	
Severe	10 (8.8)	0(0)	4(21.1)	
Autoimmune condition				0.006*
Absent	87 (77)	17(94.4)	9(47.4)	
Suspected	11 (9.7)	1(5.6)	4(21.1)	
Confirmed	15 (13.3)	0(0)	6(31.6)	
Total	113 (100)	18(100)	19(100)	
Rheumatological complaints				0.002*
Absent	83 (73.5)	18(100)	9(47.4)	
Suspected	7 (6.2)	0(0)	1(5.3)	
Confirmed	23 (20.4)	0(0)	9(47.4)	
Granulomata				0.367
Absent	109 (96.5)	18(100)	17(89.5)	
Skin only	2 (1.8)	0(0)	1(5.3)	
Lung liver spleen	2 (1.8)	0(0)	1(5.3)	
CNS eye	0 (0)	0(0)	0(0)	
Lymphoma				0.120
Absent	104 (92)	18(100)	15(78.9)	
Present	9 (8)	0(0)	4(21.1)	
Cancer (Solid Tumors)				1.0
Absent	111 (98.2)	18(100)	18(94.7)	
Present	2 (1.8)	0(0)	1(5.3)	

Group A: 18 patients who had lower severity rating (the scores were lower than mean ± SD).
Group B: 19 patients who had upper severity rating (the scores were more than mean ± SD).
* P value less than 0.05 is considered significant.
** Splenomegaly was the sole reason for all splenectomies.

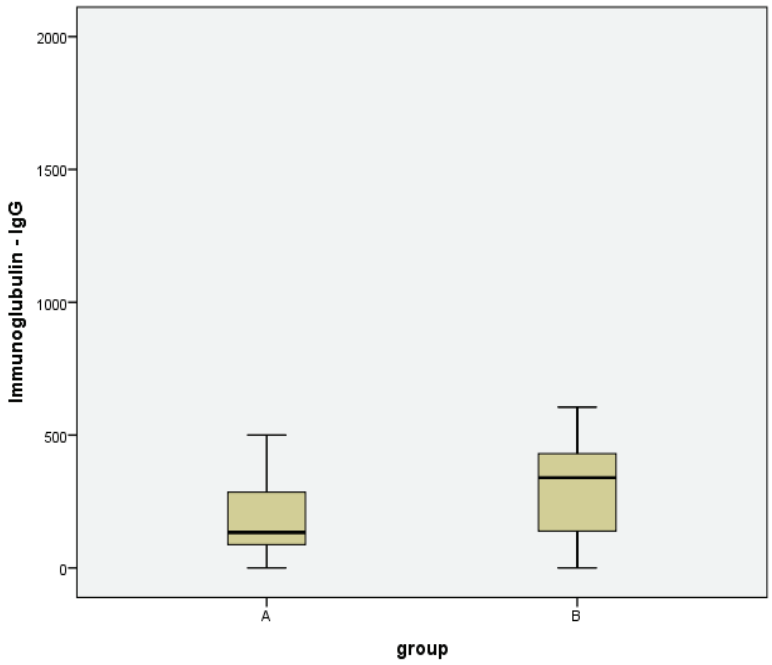

Figure 1. The boxplot of IgG in group A and B. The mean serum IgG level was significantly higher in group B (308.6 ± 195.9) compared to group A (177.8 ± 151.9; *P* = 0.03).

respectively. However, none of the correlations were significant. Patients in group B had a significantly higher percentage of CD8 lymphocytes ($P = 0.003$). Although the percentage of CD4 lymphocytes tended to be lower in group B patients, this difference was not significant ($P = 0.082$). Other immunologic characteristics for patients in group B were diminished percentage of switched memory B cells (CD27+IgM-IgD- cells in peripheral B lymphocytes, 0.5 ± 0.2 vs. 1.02 ± 0.6; $P < 0.01$) and low frequency of regulatory T cells (1.59 ± 0.42 vs. 2.17 ± 1.63; $P = 0.022$). In contrast, the analyses failed to show any difference between groups in terms of levels of immunoregulatory cytokines or radio-sensitivity.

Survival

Of all 113 patients, 36 died at the mean ± SD age of 17.79 ± 12.953 years, ranging from 1 to 59 years, at the end of the study time (Table 2). The mean ± SD age at death was equal to 18.76 ± 15.662 (range 3 to 52) years for males and 16.71 ± 9.419 (range 1 to 36) years for females ($P = 0.064$). Considering the patients labeled as group A, 16 cases were alive, yet 9 out of 19 patients in group B were not alive at the time of study. As expected, higher mortality rate was correlated with higher severity ($P = 0.029$), although no similar result was obtained from comparison of means ± SD of age at death (35 ± 15.55 years for group A vs. 17.25 ± 5.8 years for group B; $P = 0.154$). Median of survival time was 26 years in group A and 14 years in group B ($P = 0.146$). In addition, our results indicated respiratory failure, most commonly from chronic lung disease, followed by lymphoma, overwhelming infections and diseases of the liver as the prevailing causes of death in this cohort (data not shown). In our study, five patients died due to liver failures that were suffering from cirrhosis of the liver. The cause of cirrhosis in two patients was HCV.

Discussion

Common variable immune deficiency (CVID) as a heterogeneous disorder is not fully understood yet and the patients present a wide spectrum of clinical complications. Unfortunately, efforts to demonstrate any correlation between demographic and laboratory factors and disease severity have not yet led to consistent results. Some authors have tried to sub-classify CVID subjects to better investigate their outcomes and have shown that the prognosis varies with presence or absence of different manifestations. Since there was not a similar study about severity scoring system for CVID patients, we could not compare our findings with other results.

CVID is the most common symptomatic PID with a prevalence of approx. 1:91000 in our region.[23] Here, we compared the CVID patients with a Grimbacher CVID - disease severity score lower than mean ± SD (group A) and higher than mean ± SD (group B). A survey in Children's Medical Center Hospital during a period of 30 years (1984–2014) showed that diagnostic delay is a major concern in CVID patients, which could result in irreversible complications and mortality, while early diagnosis and proper initial treatment lead to better outcomes and quality of life.[24] Although our study showed higher diagnostic delay in group B with more severe disease than group A, this difference was not statistically significant. This finding is compatible with what Chapel *et al.* had shown in a study investigating a cohort of 334 patients.[4] Parental consanguinity is a known risk factor for PID with autosomal recessive pattern of inheritance.[25,26] Most of known genes involved in the pathogenesis of CVID also have the same pattern including *CD19, CD20, CD21, CD81, ICOS, TACI, BAFFR* and *LRBA*.[27–33] In Iran, parental consanguinity is reported in 72% of patients suffering from CVID, while the mean proportion of consanguineous marriages in the country is 38%.[23]

In our study, 61% of CVID patients were found to be born from a consanguineous marriage. This data is particular to areas of higher percentage of consanguinity so it is not generalizable to other countries. Due to the high rate of consanguineous marriage in Iran, autosomal recessive diseases and homozygous mutations are also more common in Iran. Thus, the disease is more severe in Iran. According to the clinical and prognostic classification proposed by Chapel *et al*, CVID patients with consanguineous parents are expected to have a shorter survival.[4] However in this study, consanguinity rate in group B was not significantly higher than group A. Among the population with CVID, 51% have a family history of PID.[23] In our study, 16.8% of patients had a positive family history of PID.

Furthermore, among the population suffering from CVID, 51% have a family history of this or other types of PID. In our study, 19% of subjects had at least one first degree relative with a documented PID and still no relevancy was detected between any family histories of susceptible- i.e., recurrent infections, early age of death, autoimmunity and malignancy- or definite PID and developing serious forms of CVID.

Resnick *et al*. detected that lower baseline serum levels of IgG and higher levels of IgM were associated with poorer survival. Lower levels of IgG or IgA significantly increased the odds ratio for development of any complication. In contrast, higher baseline serum IgM levels were associated with increased risk of lymphoma or any form of hepatitis.[34] Surprisingly, our results have indicated that IgG level is significantly higher in group B than group A. Higher IgM and low IgA level were recorded in group B but the difference was not significant. Patients with low level of immunoglobulin are prone to infectious presentations, and can be easily treated by replacing intravenous immunoglobulin (IVIG), but high levels of IgM and IgG could be associated with many autoimmune diseases.[35–37] It seems that the high level of IgG and IgM in group B might be autoantibodies that lead to autoimmune diseases or immunodysregulation. This group of patients, despite regular treatment, will have continuing complications. Low peripheral B cells are associated with reduced survival in CVID.[38] It has been demonstrated that marked depletion in CD4+ naïve T cells, massive T-cell activation, apoptosis, proliferation, and disruption of CD4+ and CD8+ TCR repertories are associated with a more severe clinical phenotype.[39,40] Our study had similar results: patients in group B had a lower percentage of CD19 and CD4 lymphocytes.

The total mortality rate in this cohort during the study period was 31% which is highly greater in more severe conditions, whilst not related to sex. Lung disease followed by lymphoma, as reported in other surveys, were the prevalent causes of death. While emerging infections are prohibited by Ig replacement and preventive antibiotic therapies, diminished survival is clearly seen in the presence of selected but not all complicated manifestations.

In conclusion, baseline parameters, as outlined here and elsewhere, can help predict the prognosis. Significant results from our survey were higher level of IgG, higher percentage of CD8 lymphocytes, diminished percentage of switched memory B cells and low frequency of regulatory T cells in CVID patients with severe complication (group B) than CVID patients with lower severity complications (group A), suggesting that these laboratory factors might be responsible for manifestation of severe complications. Knowing demographic and clinical or laboratory factors could contribute to the determination of severity in the disease and also provide better care and follow up for high-risk patients who have those factors. However, further studies are needed to definitely specify all possible clues to determine the clinical outcome more precisely.

Conflict of interest

We hereby declare that there is no conflict of interest regarding this manuscript.

Note: There is not any acknowledgment in this manuscript.

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