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ORIGINAL ARTICLE

Low Platelet Level May be a Predictor for Mortality in Adult Patients with Common Variable Immune Deficiency

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Abstract

Background: Common variable immunodeficiency (CVID) is the most common symptomatic immunodeficiency in adults. We, therefore, aimed to reveal mortality rates, causes of mortality in CVID patients, as well as demographic and clinical characteristics and differences of survived and dead CVID patients

Methods: The study group included 50 patients [(Female: 23 (46%), Male: 27 (54%)] with CVID, who were followed up on a regular basis for a period of ten years (115.18 ± 80.74 months).

Results: Diagnostic delay was 84 (0-360) months, and the mean follow-up time was 115.18 ± 80.74 months. The most common clinical presenting complaints were frequent and recurrent infections and pneumonia. At diagnosis, serum IgG levels were 1.72 (0.33 – 6.90) g/L. The overall survival rate of the patients during the follow-up time was 88%. As a result of univariate Cox regression analysis, platelet count was determined to be an independent risk factor for mortality in CVID patients (Hazard ratio, HR: 0.990, 95% confidence interval, CI: 981-0.999, p: 0.025). When the patients were classified according to mean platelet counts (platelets < 207770/mm3 and platelets > 207770/mm3), the mortality rate in the patient group with platelets < 207770/mm3 was determined to be statistically significantly higher compared to the patient group with platelets > 207770/mm3 (log-rank: 0.013).

Conclusions: Clinicians dealing with this patient group should remember that immune dysregulation and low platelet count are independent risk factors for mortality and they should remarkably follow up patients with low platelet count closely.

Keywords: Platelets, Common Variable Immune Deficiency, Mortality.

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INTRODUCTION

Common variable immunodeficiency (CVID) is the most common symptomatic immunodeficiency in adults (1). The expression "variable" included in the name defines the heterogeneity of manifestations. The patients suffer from frequent and recurrent infections and disorders affecting several organs and systems, including chronic pulmonary disease, immune dysregulation, autoimmunity, lymphoproliferation, granulomatous diseases, and tendency to malignancies. Diagnosis of CVID is established by low levels of serum IgG together with low levels of IgM and/or IgA, poor vaccine response, and exclusion of secondary causes that may lead to immunodeficiency (2, 3). Its prevalence is considered to be between 1:25.000 and 1:50.000 (4). Although CVID may develop at any age, its findings peak at childhood and early adulthood (5). Due to insufficient awareness of physicians on this issue and reasons such as consideration of primary immunodeficiencies as childhood diseases, the diagnostic delay is, unfortunately, common (6). CVID patients have increased mortality compared to the normal population because of infectious and non-infectious complications (7). In several studies, CVID-related mortality has been shown to vary between 15% to 29% (5, 7, 8). Owing to the reduction of mortality caused by infections with immunoglobulin replacement therapy (IGRT), chronic complications such as chronic pulmonary diseases and malignancies have become significant causes of mortality (9). In previous studies, lymphoid malignancies and autoimmunity have been independent risk factor for mortality and emphasized that autoimmune cytopenia is associated with increased prevalence of bronchiectasis, morbidity, and mortality (10, 11). Thus, the demonstration of risk factors and causes of mortality in this patient group is crucial for both diagnosis of the patients and the treatment of complications.

Therefore, we aimed to reveal mortality rates, causes of mortality in CVID patients who were being followed-up in our clinic, demographic and clinical characteristics and differences of survived and dead CVID patients, and the effect of platelet counts on mortality in these patients.

MATERIALS AND METHODS

The study group included 50 patients with CVID who were followed up on a regular basis for a period of ten years (115.18 ± 80.74 months). Diagnosis of CVID was made according to updated diagnostic criteria of ESID (European Society for Immunodeficiencies) (3). In that cross-sectional study, patient records of who were being followed up with a diagnosis of CVID between 2010 and 2020 were reviewed. Patients' demographic data (including current age, gender, age at diagnosis, diagnostic delay, consanguinity, smoking status, type of immunoglobulin replacement therapy, the status of prophylactic antibiotic use) and clinical characteristics at diagnosis (presence of severe lymphopenia, presence of bronchiectasis, presence of splenomegaly, spirometry results, complete blood count parameters, serum immunoglobulin levels, and peripheral lymphocyte subsets) were obtained from their files. The lymphocyte count <1000 cells/mm^3 was considered severe lymphopenia.

Complete blood count was measured with Sheath reagent by Abbott Cell Dyn 3700 series (Chicago, USA). Quantitative determination of serum IgG, IgM, IgA, and IgE was made by means of particle-enhanced immunonephelometry using the Siemens BN II/ BN ProSpec system (Erlangen, Germany). Peripheral blood lymphocyte subsets were measured using the BD FACS Canto II 8-color configuration flow cytometer system (New Jersey, USA) with fluorescently labeled antibodies.

Spirometric measurements were obtained using a common protocol with the nSpire ZAN 100 spirometer. Three maneuvers were performed, although additional tests may be needed if one or more of the curves are unacceptable. The forced expiratory volume in one second (FEV1), the ratio of FEV1/FVC (forced vital capacity), peak expiratory flow (PEF), and mean expiratory flow 25%-75% of predicted values for similar age, sex, race, and height were recorded.

The study protocol was approved by the Necmettin Erbakan University Meram Medical Faculty Ethics Committee (Date: 03.04.2020 – No: 2020/2401). This study was performed according to the ethical standards laid down Declaration of Helsinki and its later amendments. The authors carried out no animal or human studies for this article.

Statistical analysis was performed with IBM SPSS Statistics Version 22 software package. Normally distributed parameters were presented as mean ± standard deviation, and data that is not normally distributed were expressed as median (minimum-maximum). While Pearson correlation analysis was used for normally distributed parameters,

Spearman rank correlation analysis was used for non-parametric variables. Descriptive data were presented as frequencies and percentages and compared using the Chi-square test. Comparisons between baseline characteristics were performed by independent Student t, Mann-Whitney rank-sum, Fisher exacts, or Chi-square tests where appropriate. Binomial logistic regression analysis was performed to determine independent predictors for mortality. To determine independent predictors for mortality Cox regression analysis and Kaplan Meiers test were performed.

RESULTS

Fifty CVID patients [(Female: 23 (46%), Male: 27 (54%)] were included in the study. Of the study population, the median age was 37 (23-67) years, and the age at diagnosis was 27.94 ± 13.64 years. The diagnostic delay was 84 (0-360) months, and the mean follow-up time was 115.18 ± 80.74 months. The most common clinical presenting complaints were frequent and recurrent infections and pneumonia.

Of the patients, 30% had severe lymphopenia, 56% splenomegaly, and 60% bronchiectasis. At diagnosis, serum IgG levels were 1.72 (0.33 – 6.90) g/L and switched memory B cell percentages 1.70 (0 – 52.0). The overall survival rate of the patients during the follow-up time was 88%. The Demographic, clinical, and laboratory characteristics of the study population were summarized in Table 1.

Table 1. Baseline demographic, clinical, and immunological parameters of the study population

Demographic properties		Clinical and Immunological parameters	
Gender, Female, n (%)	23 (46)	Neutrophil count, mm^3	3660 (1000-12500)
Current age, year	37 (23-67)	Lymphocyte, mm^3	1445 (400-8900)
Age at diagnosis, year	27.94 ± 13.64	Platelet count, mm^3	207770 ± 96657
Diagnostic delay, month	84 (0-360)	Neutrophil / lymphocyte ratio	2.45 (0.74-7.50)
Follow-up time, month	115.18 ± 80.74	Platelet / lymphocyte ratio	114.82 (9.08 – 607)
Consanguinity, n (%)	22 (44)	IgG, g/L	1.72 (0.33 – 6.90)
Smoking, n (%)	7 (14)	IgM, g/L	0.26 (0.06 – 5.99)
SCIG, n (%)	14 (28)	IgA, g/L	0.24 (0 – 190)
Severe lymphopenia, n (%)	15 (30)	IgE, g/L	17 (5-220)
Bronchiectasis, n (%)	30 (60)	$CD3^+$ T cells, %	76.54 ± 11.47
Low FEV1, n (%)	25 (50)	$CD4^+$ T cells, %	31.66 ± 14.32
Malignancy, n (%)	3 (6)	$CD8^+$ T cells, %	37.50 (19-74)
Prophylaxis, n (%)	38 (76)	$CD19^+$ B cells, %	7.10 ± 5.95
BMI	25.75 (14.80-49.0)	$CD16^+$ - 56^+ NK cells, %	7.50 (0 – 26.0)
FEV1	72.17 ± 17.68	IgM^- $CD27^+$ Switched Memory B cells, %	1.70 (0 – 52.0)
FEV1 / FVC	98.02 ± 10.12	IgM^+ $CD27^-$ Naive B cells, %	84.55 (0-98.60)
PEF	66.50 (3.80 – 100)	Mortality	6 (12)
MEF25-75	59.53 ± 25.15	Splenomegaly, n (%)	28 (56)

CVID: Common variable immune deficiency, Ig: immune globulin, SCIG: subcutaneous immune globulin, CD: The cluster of differentiation, FEV1: The forced expiratory volume in 1 second, FVC: forced vital capacity, PEF: The peak expiratory flow, MEF25-75: the mean expiratory flow between the 25% and 75% of the FVC

When the patients who survived and died during follow-up time were compared, there was no significant difference between the groups in regard to gender, duration of diagnostic delay, serum IgG level at diagnosis, CD19+ B cell and IgM- CD27+ Switched Memory B cell percentages, as well as the presence of severe lymphopenia, splenomegaly, bronchiectasis, and malignancy. There was a statistically significant difference in regard to the current age, age at diagnosis, IgM levels at diagnosis, platelet counts and platelet/lymphocyte ratio (p: 0.039, p: 0.049, p: 0.041, p: 0.011, p: 0.042 and p: 0.019, respectively). A comparison of demographic, laboratory and immunological parameters of survived and dead CVID patients was summarized in Table 2.

Table 2. Comparison of demographic, clinical and laboratory parameters of CVID patients who died and survived

	Dead (N=6)	Alive (N: 44)	p
Gender, F, n (%)	1 (16.7)	22 (50)	0.124
Current age, years	61 (59-63)	36.5 (23-67)	**0.039**
Age at diagnosis	38.17 ± 17.31	26.55 ± 12.67	**0.049**
Diagnostic delay, month	48 (0-120)	84 (0-360)	0.211
Follow up time, month	127.17 ± 83.08	105.09 ± 94.33	0.702
Consanguinity, n (%)	2 (33.3)	20 (45.5)	0.746
Smoking, n (%)	0	7 (16.3)	0.329
SCIG, n (%)	0	14 (31.8)	0.103
Severe lymphopenia, n (%)	2 (33.3)	13 (29.5)	0.849
Splenomegaly, n (%)	4 (66.7)	24 (54.5)	0.575
Bronchiectasis, n (%)	5 (83.3)	25 (56.8)	0.214
Malignancy, n (%)	0	3 (6.8)	0.509
Prophylaxis, n (%)	4 (66.7)	34 (77.3)	0.568
BMI	28.6 (28.19-29)	24.68 (14.80-49)	0.151
Neutrophil count, mm^3	1450 (1000-1900)	3825 (1058- 12500)	0.388
Lymphocyte count, mm^3	1100 (1000-1200)	1520 (400-8900)	0.404
Platelet count, mm^3	115333 ± 103511	220375 ± 89697	**0.011**
Neutrophil / Lymphocyte ratio	1290 (1.0-1.58)	2590 (0.74- 7.50)	0.439
Platelet / lymphocyte ratio	51.92 (50.83- 53.0)	119.15 (9.08-607)	**0.042**
FEV1, %	61.33 ± 15.28	73.04 ± 17.75	0.275
FEV1/FVC	97.67 ± 13.61	98.05 ± 10.03	0.951
PEF	42.4 (3.80-81.0)	66.5 (5.39 – 100.0)	0.401
MEF 25/75	67.33 ± 28.50	59.01 ± 25.19	0.588
IgG at diagnosis, g/L	1.96 (1.17-2.75)	1.72 (0.33- 6.90)	0.886
IgM at diagnosis, g/L	0.26 (0.09-0.44)	0.26 (0.06 – 5.99)	**0.041**
IgA at diagnosis, g/L	0.09 (0.07- 0.11)	0.25 (0-1.90)	0.116
IgE at diagnosis, IU/mL	5 (5-5)	17.25 (5-220)	0.568
$CD3^+$ T cells, %	78.60 ± 7.34	76.31 ± 11.89	0.677
$CD4^+$ T cells, %	28.00 ± 24.63	32.08 ± 13.07	0.552
$CD8^+$ T cells, %	31 (19-43)	37.5 (19-74)	0.357
$CD19^+$ B cells, %	7.60 ± 7.63	7.05 ± 5.84	0.846
$CD16^+$- 56^+ NK cells, %	11 (7-15)	7.50 (0-26)	0.449
IgM^- $CD27^+$ Switched Memory B cells, %	0.05 (0-0.10)	2.20 (0-52.0)	0.472
IgM^+ $CD27^-$ Naive B cells, %	93.20 (90-96.40)	83.50 (0-98.60)	0.256

CVID: Common variable immune deficiency, Ig: immune globulin, SCIG: subcutaneous immune globulin, BMI: Body mass index, CD: The cluster of differentiation, FEV1: The forced expiratory volume in 1. second, FVC: forced vital capacity, PEF: The peak expiratory flow, MEF25-75: the mean expiratory flow between the 25% and 75% of the FVC, CD: The cluster of differentiation

As a result of univariate Cox regression analysis, platelet count was determined to be an independent risk factor for mortality in CVID patients (Hazard ratio, HR: 0.990, 95% confidence interval, CI: 981-0.999, p: 0.025) (Table 3 and Table 4). As a result of multivariate Cox regression analysis; current age, BMI, and neutrophil/lymphocyte ratio were not found to be independent predictors for mortality, whereas platelet count was determined to be an independent predictor for mortality (HR: 0.990, CI: 0.981-0.999, p: 0.025) (Table 5). When the patients were classified according to mean platelet counts (platelets < 207770/mm^3 and platelets > 207770/mm^3), the mortality rate in the patient group with platelets < 207770/mm^3 was determined to be statistically significantly higher compared to the patient group with platelets > 207770/mm^3 (log-rank: 0.013) (Figure 1). The most common causes of mortality of the patients were pneumonia and pneumonia-induced sepsis (Figure 2).

Table 3. Univariate Cox regression analyses demonstrating the relationship between demographic characteristics and mortality in CVID patients

Variables	Univariate Analysis	
	HR (95% CI)	P value
Gender	3.527 (0.410 -30.323)	0.251
Age	1.043 (0.983 -1.106)	0.165
Diagnostic delay	0.992 (0.977-1.007)	0.308
Consanguinity	1.418 (0.446-4.321)	0.539
Smoking	0.039 (0 -2817.666)	0.571
BMI	0.902 (0.773-1.054)	0.194
Severe lymphopenia	1.672 (0.302-9.261)	0.556
Splenomegaly	0.900 (0.378-2.147)	0.813
Bronchiectasis	2.307 (0.266-20.021)	0.448
Malignancy	4.87 (0.009-2761.254)	0.624
Prophylaxis	2.827 (0.519-15.407)	0.230

CVID: Common variable immune deficiency, BMI: Body Mass Index

Table 4. Univariate Cox regression analyses demonstrating the relationship between laboratory and immunological parameters and mortality in CVID patients

Variables	Univariate Analysis	
	HR (95% CI)	P value
Neutrophil count	1.000 (1.000-1.000)	0.451
Lymphocyte count	1.000 (0.999-1.000)	0.379
Platelet count (× 10^3)	0.990 (0.981-0.999)	**0.02**5
Neutrophil/ lymphocyte ratio	1.059 (0.988 -1.136)	0.106
Platelet/ lymphocyte ratio	1.002 (0.995-1.008)	0.619
FEV1	0.969 (0.916-1.024)	0.267
FEV1 / FVC	1.007 (0.889-1.140)	0.918
IgG level, at diagnosis	0.926 (0.587 -1.461)	0.741
IgM level, at diagnosis	0.119 (0-70.426)	0.513
IgA level, at diagnosis	0.023 (0- 19.171)	0.272
IgE level, at diagnosis	0.969 (0.859-1.094)	0.615
CD3$^+$ T cells, %	1.015 (0.940-1.096)	0.700
CD4$^+$ T cells, %	0.982 (0.902-1.068)	0.688
CD8$^+$ T cells, %	1.010 (0.949-1.076)	0.749
CD19$^+$ B cells, %	1.020 (0.883-1.178)	0.786
CD16$^+$ - 56$^+$ NK cells, %	0.933 (0.816-1.067)	0.313
IgM$^-$ CD27$^+$ Switched Memory B cells, %	0.982 (0.866-1.115)	0.784
IgM$^+$ CD27$^-$ Naive B cells, %	1.127 (0.861-1.475)	0.383

CVID: Common variable immune deficiency, BMI: Body Mass Index, Ig: immune globulin, SCIG: subcutaneous immune globulin, CD: The cluster of differentiation, FEV1: The forced expiratory volume in 1 second, FVC: forced vital capacity, PEF: The peak expiratory flow, MEF25-75: the mean expiratory flow between the 25% and 75% of the FVC

Table 5. Multivariate Cox regression analyses demonstrating the relationship between baseline characteristics and mortality in CVID patients

Variables	Multivariate Analysis	
	HR (95% CI)	P value
Age	1.013 (0.948-1.083)	0.706
BMI	0.898 (0.714-1.130)	0.360
Platelet count (× 10^3)	0.990 (0.981-0.999)	**0.025**
Neutrophil/ lymphocyte ratio	0.973 (0.880-1.076	0.594

CVID: Common variable immune deficiency, BMI: Body Mass Index

Figure 1. The mortality rate in the patient groups with platelets < 207770/mm3 and platelets > 207770/mm3

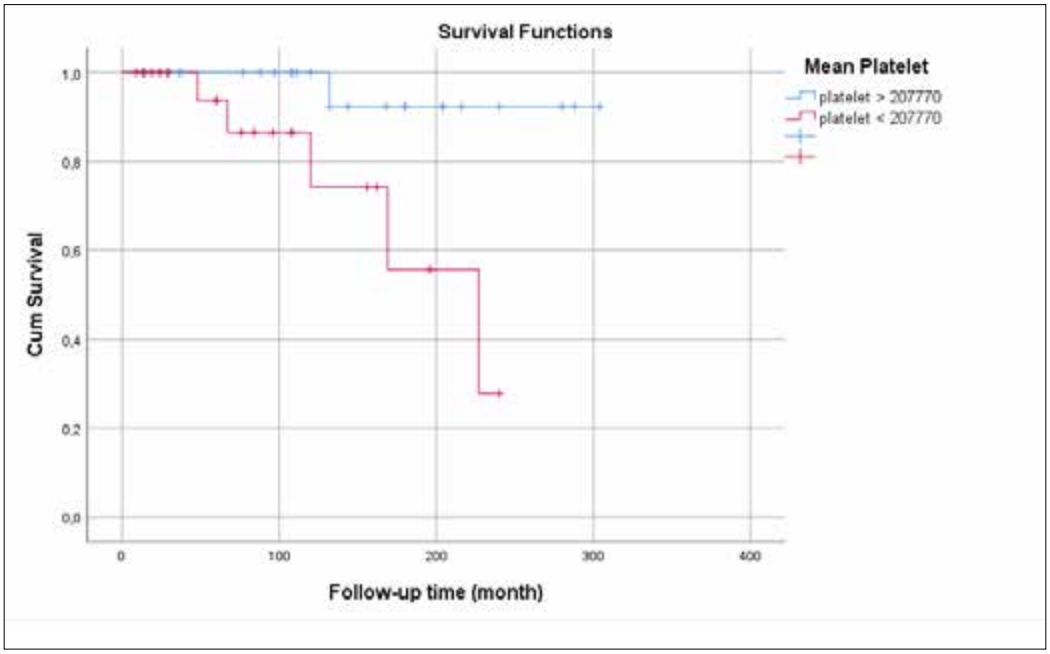
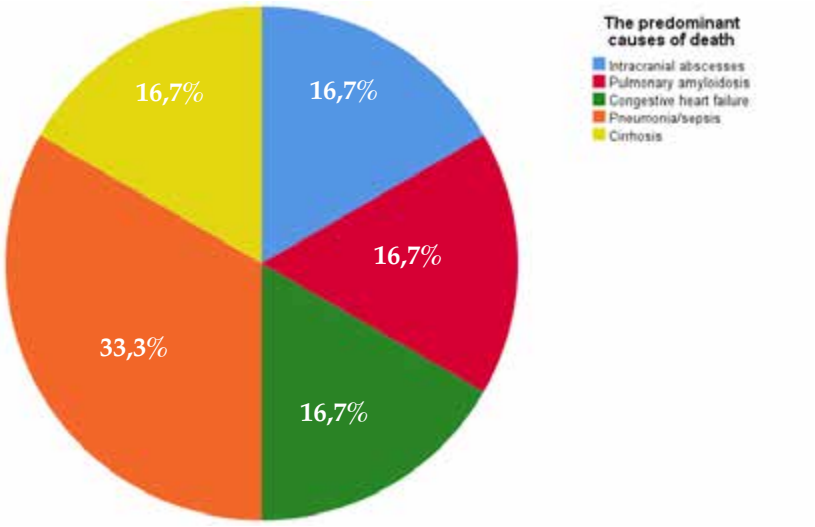


Figure 2. The predominant causes of death



DISCUSSION

Common variable immunodeficiency is the most common symptomatic primary immunodeficiency in adults (1). In addition to frequent and recurrent respiratory tract infections, patients may present with disorders with immune dysregulation. While infection-related mortality rates have been decreasing owing to immunoglobulin replacement therapy in this patient group, complications of other systems and malignancies have become a significant cause of mortality. In our study, the overall survival rate of the patients was found to be 88%. Furthermore, a lower platelet count was determined to be an independent risk factor for mortality.

B cell defects characterize CVID, and poor vaccine response makes the patients vulnerable to respiratory tract infections with encapsulated bacteria. A study of 224 CVID patients by Quinti et al. (12) reported respiratory tract infections as the most prominent clinical problem both at diagnosis and during the follow-up time. In a 2007 study by Aghamohammadi et al. (5), they reported that the most common cause of mortality in CVID patients was respiratory insufficiency and that the 20-year mortality rate of the patients was 27%. In a study by Gathmann et al. (10), the most common clinical presentation in CVID patients was reported to be pneumonia at a rate of 32%. The fact that our patients' most common clinical presentation was pneumonia and upper respiratory tract infections is consistent with the literature.

Mortality in the CVID patient group is higher compared to the normal population. Although infection-related mortality rates have been reduced with immunoglobulin replacement therapy, mortality due to malignancies and organ complications are still problematic. In a study by Cunningham-Rundles et al. (7), the 20-year mortality rate was reported as 36% in male CVID patients and 33% in female CVID patients. In a study by Resnick et al. (9) the mortality rate during a 40-year follow-up time was found to be 19.6%. The median age of death was reported as 44 years in females and 42 years in males. In another study, Quinti et al. (13) reported mortality during a 40-year follow-up time as 19.5% and the median age of death as 54 years, and the primary cause of mortality was reported to be chronic pulmonary diseases (30%). In our current study, the 10-year mortality rate was determined to be 12% (with an overall survival rate of 88%). The most common cause of mortality, however, was pneumonia and pneumonia-related sepsis. Although our mortality rate was supposed to be lower due to both smaller population and relatively shorter follow-up time of our study compared to aforementioned studies, the fact that our study was recently conducted, therefore, reduction of difficulties in availability of the patients to immunoglobulin replacement therapy and appropriate antibiotics, and advancements in diagnosis and treatment may have lowered the mortality rates.

Immune dysregulation is an important complication in CVID patients. Autoimmunity is a sign of immune dysregulation, and autoimmune complications may be the presenting symptom in 25% of the patients (14). The coexistence of immunodeficiency with autoimmunity may be considered paradoxical. Because there are poor responses to pathogens and vaccines in CVID and immunoglobulin levels are low; however, autoantibody reproduction may be increased simultaneously. Self-tolerance is impaired due to the presence of autoreactive B and T cells. Disorders of innate and adaptive immunities may lead to abnormal B cell clones and the secretion of abnormal cytokines. All these associations may lead to the coexistence of immunodeficiency with autoimmune conditions (15). The most common autoimmune complications in CVID are cytopenias, particularly immune thrombocytopenia (16). In the USIDNET (The United States Immunodeficiency Network) registry system, patients with autoimmune cytopenias have been determined to be associated with non-infectious complications, including lymphoproliferation and granulomatous disorders enteropathy, lymphoma, and interstitial pulmonary diseases (16). In another study, reduced platelet count and switched memory B cell ratio was reported to be a risk factor for bronchiectasis (17). Fisher et al. (18) reported that autoimmune conditions negatively affect the overall survival rate. In a study of 334 CVID patients, Gathmann et al. (10) reported lymphoid malignancies and autoimmunity as independent risk factors for mortality. In a study by Cunningham-Rundles et al. (11), autoimmune cytopenias were associated with increased morbidity and mortality. Also, in our study, reduced platelet count was determined to be an independent risk factor for mortality. These findings suggest that the reduction in platelet count may be an indirect indicator of increased immune dysregulation. As reduced platelet count due to increased immune dysregulation may be associated with other factors causing mortality, primarily lymphoproliferation,

granulomatous disorders, and chronic pulmonary diseases, reduced platelet count may be associated with mortality.

In conclusion, infections and infection-related sepsis remain to be a significant cause of mortality in CVID patients. Although survival rates in CVID patients are better than before, mortality rates are still higher than in the normal population. Clinicians dealing with this patient group should remember that immune dysregulation and low platelet count are independent risk factors for mortality, and they should particularly follow up patients with low platelet count closely.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

The study protocol was approved by the Necmettin Erbakan University Meram Medical Faculty Ethics Committee (Date: 03.04.2020 – No: 2020/2401). This study was performed according to the ethical standards laid down Declaration of Helsinki and its later amendments. The authors carried out no animal or human studies for this article.

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