Research Article / Araştırma Makalesi

Could the C-reactive protein/albumin Ratio Predict Mortality in Patients with Common Variable İmmunodeficiency?

C-reaktif protein/albümin Oranı Yaygın Değişken İmmün Yetmezliği Olan Hastalarda Mortaliteyi Tahmin Edebilir mi?

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Abstract: Common variable immunodeficiency (CVID) is the most common symptomatic immunodeficiency in adults. This study assessed the utility of using the C-reactive protein (CRP)/albumin ratio (CAR) at diagnosis to predict mortality in CVID patients. Between 2010 and 2022, hospital records and follow-up cards of patients with CVID were reviewed retrospectively. Seventy-five patients were included in the study. CRP 0–5 mg/L and albumin 3.5–5.5 g/dL were taken as references. The CAR was obtained by dividing the CRP value by the albumin value. Of the included patients, 41 (55%) were male and 34 (35%) were female. The median age was 38 (21–77) years. The mortality rate of the patients during the follow-up time was 20%. Of the patients, 41% had splenomegaly, 10.6% had malignancy, and 39% had bronchiectasis. The cut-off value of CAR to predict mortality was >2.18 (sensitivity: 88.4%, specificity: 90.1%). When the patients were classified according to the CAR, the mortality rate in the patient group with a CAR > 2.18 was statistically significantly higher than the patient group with a CAR ≤ 2.18. The CAR is a cheap, simple, and easily calculated parameter that can predict mortality in CVID patients.
Anahtar Kelimeler: Common Variable Immunedeficiency; Albumin; CRP

Özet: Yaygın değişken immün yetersizlik (YDİY), yetişkinlerde en sık görülen semptomatik primer immün yetmezliktir. Bu çalışma, CVID hastalarında mortaliteyi tahmin etmek için tanıda C-reaktif protein (CRP)/albümin oranı (CAO) kullanmanın faydasını değerlendirdi. 2010-2022 yılları arasında YDİY'li hastaların hastane kayıtları ve takip kartları retrospektif olarak incelendi. Çalışmaya yetmiş beş hasta dahil edildi. CRP 0–5 mg/L ve albümin 3,5–5,5 g/dL referans olarak alındı. CAO, CRP değerinin albümin değerine bölünmesiyle elde edildi. Çalışmaya alınan hastaların 41'i (%55) erkek, 34'ü (%35) kadındı. Ortanca yaş 38 (21-77) idi. Takip süresi boyunca hastaların ölüm oranı %20 idi. Hastaların %41'inde splenomegali, %10.6'sında malignite ve %39'unda bronşektazi vardı. CAO'nın mortaliteyi öngörmek için kesme değeri >2,18 idi (duyarlılık: %88,4, özgüllük: %90,1). Hastalar CAO göre sınıflandırıldığında, CAO > 2,18 olan hasta grubunda mortalite oranı, CAO ≤ 2,18 olan hasta grubuna göre istatistiksel olarak anlamlı derecede yüksekti. CAO, YDİY hastalarda mortaliteyi tahmin edebilen ucuz, basit ve kolayca hesaplanabilen bir parametredir.
Keywords: Yaygın değişken immün yetersizlik; Albumin; CRP

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1. Introduction

Common variable immunodeficiency (CVID) is characterized by impaired production of immunoglobulins (1). Most patients with CVID are diagnosed at 20–40 years of age, but 20% might be diagnosed earlier (2). Because the disease is heterogeneous, a 6- to 7-year delay in diagnosis is common (2, 3). Its prevalence is between 1:25,000 and 1:50,000 (3). Patients suffer from frequent recurrent infections and disorders affecting various organs and systems, including chronic lung disease, immune dysregulation, autoimmunity, lymphoproliferation, granulomatous diseases, and malignancies (4). At the same time, these reasons are the most important causes of mortality. However, mortality caused by infections has decreased with immunoglobulin replacement therapy (IGRT) (5). Autoimmune and inflammatory conditions have led to increased morbidity and mortality over time (3, 6). It is essential to identify the risk factors and causes of mortality for diagnosing and treating complications in this patient group.

The roles of hypoalbuminemia and elevated C-reactive protein (CRP) levels in predicting critical prognoses have been investigated extensively in septic patients, malignancies, and autoimmune diseases (7-9). However, the prognostic role of the inflammation-based biomarker CRP/albumin ratio (CAR) in CVID has yet to be investigated. For this reason, we investigated mortality rates, differences between survival and mortality in CVID patients, and the utility of CAR for predicting mortality in these patients.

2. Materials and Methods

2.1. Study design

This retrospective cohort study was conducted at Necmettin Erbakan University Meram Medical Faculty Hospital, Konya, Turkey. The study protocol was approved by the ethics committee of the university (approval number: 2023/4222). We included 78 patients with CVID who were followed regularly for 12 years. Three patients were excluded due to drug use (anti-inflammatory, antibiotic, statins, and so forth) or concurrent systemic infection in the prior week that could affect the CRP level. The diagnosis of CVID was determined according to the updated diagnostic criteria of the European Society for Immunodeficiencies (ESID) (10).

2.2. Data collection

Patient demographic data (age, sex, age at diagnosis, delay in diagnosis) and clinical features at the time of diagnosis (the presence of bronchiectasis, splenomegaly, or malignancy) were obtained from their files. Patient mortality data were obtained from the national database. Complete blood count parameters, serum levels of immunoglobulin, peripheral lymphocyte subgroups, CRP, and albumin levels were examined from the blood tests at the time of diagnosis. A CRP of 0–5 mg/L and albumin of 3.5–5.5 g/dL were taken as the reference levels. The CAR was obtained by dividing the CRP value by the albumin level.

2.2. Immunoglobulin measurements

Serum levels of IgG, IgM, IgA, and IgE were quantitatively determined via particle amplified immunonephelometry using the Siemens BN II/BN ProSpec system (Erlangen, Germany).

2.3. Flow cytometry analysis

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.

2.4. Statistical analysis

Continuous variables are presented as means ± the standard deviation or the medians (min-max), and categorical variables are given as numbers with percentages. We compared the data using the independent-sample t-test when the parametric test assumptions were met. In all other cases, the Mann-Whitney U test was employed. Descriptive data are presented as frequency and percentages and were compared using the chi-square test. The optimal cut-off point was selected according to the receiver operating curve (ROC) analysis. The survival curves were generated

using the Kaplan-Meier analysis and evaluated using the log-rank test. Univariate and multivariate analyses were performed using the Cox regression model to determine the independent prognostic factors.

3. Results

We enrolled 75 patients with a median age of 38 (21–77) years; 45.3% (n = 34) were female, and 54.7% (n = 41) were male. The age at diagnosis was 29 (4–72), the delay in diagnosis was 60 (0–360) months, and the median follow-up period was 108 (12–324) months. The most common clinical presenting complaints were frequent and recurrent infections and pneumonia.

Of the patients, 41% had splenomegaly, 10.6% had malignancy, and 39% had bronchiectasis. The mortality rate of the patients during the follow-up time was 20%. At diagnosis, CRP levels were 5.44 (0.3–25) mg/L, albumin levels were 4.1 (1.9–4.9) g/L, and the CAR was 1.51 (0.06–9.2). The demographic, clinical, and laboratory characteristics of the study population are summarized in Table 1.

A comparison of patients who survived and those who died during the follow-up period showed no significant difference between the groups regarding the diagnosis delay time, immunoglobulin levels at the time of diagnosis, splenomegaly, and bronchiectasis. There was a statistically significant difference for malignancy, CRP, albumin, CAR, $CD3^+$ T cells, $CD4^+$ T cells, and $CD27^+$ switched memory B cells percentages ($p < 0.05$). Table 2 compares the demographic and immunological parameters of CVID patients who survived and those who died.

The univariate Cox regression analysis revealed that age at diagnosis (HR: 1.04, CI: 1.01-1.08, p: 0.008), malignancy (HR: 0.29, CI:0.09-0.94, p: 0.039), $CD3^+$ T cells (HR: 0.96, CI:0.93-0.99, p: 0.038), $CD4^+$ T cells (HR: 0.95, CI:0.91-1.0, p: 0.05), CRP (HR: 1.17 CI:1.08-1.26, p: <0.001), albumin (HR: 0.15, CI:0.07-0.31, p: <0.001), and CAR (HR: 1.62, CI:1.33-1.97, p: <0.001) were independent risk factors for mortality in CVID patients. The multivariate Cox regression analysis showed that malignancy, $CD3^+$ T cells, and $CD4^+$ T cells were not independent predictors for mortality, whereas age at diagnosis (HR: 1.06, CI: 1.01-1.11, p:0.008) and albümin (HR:0.06, CI: 0.006-0.56, p:0.014) were independent predictors for mortality. (Table 3).

The cut-off value of the CAR to predict mortality was > 2.18 (sensitivity: 88.4%, specificity of 90.1%). When the patients were classified according to the CAR (CAR ≤ 2.18 and CAR > 2.18), the mortality rate in the patient group with a CAR > 2.18 was statistically significantly higher compared to the patient group with a CAR ≤ 2.18 (log-rank: < 0.001) (Figure 1).

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

Sex, female, n (%)	34 (45.3)	IgA, g/L	0.26 (0–4)
Current age, years	38 (21–77)	IgE, IU/mL	17.8 (5–344)
Age at diagnosis, years	29 (4–72)	$CD3^+$ T cells, %	76.38 ± 11.96
Diagnostic delay, months	60 (0–360)	$CD4^+$ T cells, %	32.34 ± 13.9
Follow-up time, months	108 (12–324)	$CD8^+$ T cells, %	40 (15–77)
Bronchiectasis, n (%)	29 (38.7)	$CD19^+$ B cells, %	6 (0–28)
Malignancy, n (%)	8 (10.6)	$CD16^+$–56^+ NK cells, %	7 (0–53)
Splenomegaly, n (%)	31 (41.3)	IgM- $CD27^+$ switched memory B cells, %	3 (0–57)
Mortality, n (%)	15 (20)	CRP (mg/L)	5.44 (0.3–25)
IgG, g/L	3.6 (0.3–6.9)	Albumin (g/dL)	4.1 (1.9–4.9)
IgM, g/L	0.32 (0.06–5.9)	CRP/albumin ratio	1.51 (0.06–9.2)

Abbreviations: CRP, C-reactive protein

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

	Death (n = 15)	**Alive (n = 60)**	**P-value**
Gender, n (%)			0.297
Female	5 (33.3)	29 (48.3)	
Male	10 (66.7)	31 (51.7)	
Current age, years	42 (21–66)	37.5 (22–77)	0.503
Age at diagnosis, years	31 (13–60)	27 (4–72)	0.241
Diagnostic delay, months	60 (0–294)	60 (0–360)	0.915
Follow-up time, month	84 (12–300)	108 (12–324)	0.124
Bronchiectasis, n (%)	7 (46.7)	22 (36.7)	0.477
Malignancy, n (%)	5 (33.3)	3 (5)	**0.026**
Splenomegaly, n (%)	8 (53.3)	23 (38.3)	0.291
IgG, g/L	2.77 (0.33–6.71)	3.6 (0.33–6.9)	0.556
IgM, g/L	0.2 (0.09–5.99)	0.32 (0.06–5.72)	0.691
IgA, g/L	0.23 (0.06–1.76)	0.26 (0–4)	0.061
IgE, g/L	17.6 (5–55.9)	18 (5–344)	0.432
$CD3^+$ T cells, %	68.5 ± 13.1	78.35 ± 10.9	**0.002**
$CD4^+$ T cells, %	25.6 ± 17.3	34 ± 12.5	**0.031**
$CD8^+$ T cells, %	39 (19–71)	40.5 (15–77)	0.786
$CD19^+$ B cells, %	3 (0–21)	6.9 (0–28)	0.705
$CD16^+$–56^+ NK cells, %	6 (1–42)	7 (0–53)	0.847
IgM- $CD27^+$ switched memory B cells, %	0.8 (0–17)	3.45 (0–57)	**0.029**
CRP (mg/L)	15.2 (4.1–25)	4.6 (0.3–18.7)	**<0.001**
Albumin (g/L)	2.8 (1.9–3.9)	4.2 (3–4.9)	**<0.001**
CRP /albumin ratio	6.03 (1.39–9.26)	1.15 (0.06–5.15)	**<0.001**

Abbreviations: CRP, C-reactive protein

Table 3. Univariate and multivariate analyses of overall survival using the Cox proportional hazard model.

Variable	**Univariate analysis**			**Multivariate analysis**		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age at diagnosis, years	1.04	1.01–1.08	**0.008**	1.06	1.01–1.11	**0.008**
Diagnostic delay, months	0.99	0.99–1.00	0.847			
Bronchiectasis, n (%)	1.26	0.43–3.67	0.663			
Malignancy, n (%)	0.29	0.09–0.94	**0.039**	1.00	0.14–6.99	0.994
Splenomegaly, n (%)	0.59	0.21–1.65	0.321			
IgG, g/L	0.97	0.74–1.27	0.870			
IgM, g/L	1.19	0.84–1.68	0.315			
IgA, g/L	0.56	0.17–1.84	0.346			
IgE, g/L	0.56	0.97–1.01	0.568			
$CD3^+$ T cells, %	0.96	0.93–0.99	**0.038**	0.99	0.92–1.06	0.883
$CD4^+$ T cells, %	0.95	0.91–1.00	**0.05**	0.96	0.9–1.02	0.275
$CD8^+$ T cells, %	0.99	0.95–1.03	0.726			
$CD19^+$ B cells, %	0.99	0.96–1.06	0.793			
$CD16^+$–56^+ NK cells, %	1.00	0.96–1.05	0.736			
IgM- $CD27^+$ switched memory B cells, %	0.92	0.83–1.01	0.103			
CRP (mg/L)	1.17	1.08–1.26	**< 0.001**	1.28	0.81–2.04	0.281
Albumin (g/L)	0.15	0.07–0.31	**< 0.001**	0.06	0.006–0.56	**0.014**
CRP /albumin ratio	1.62	1.33–1.97	**<0.001**	0.55	0.141–2.16	0.395

Abbreviations: CRP/albumin ratio, C-reactive protein to albumin ratio; HR, Hazard ratio; CI, confidence interval.

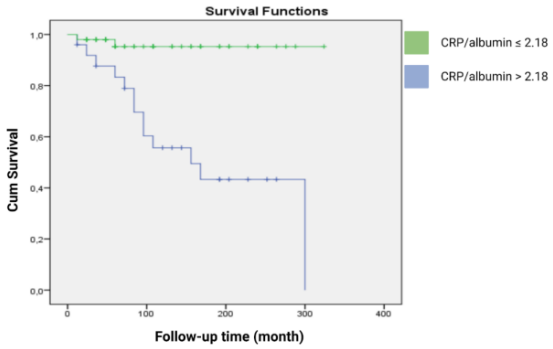

Figure 1. Mortality rates in patient groups with CRP/albumin ≤ 2.18 and CRP/albumin > 2.18.

4. Discussion

We found that CAR is an independent predictor of mortality in CVID, and mortality is higher in patients with a CAR >2.1. Previous studies have investigated the effectiveness of the CAR as a prognosis and mortality marker, particularly in malignant diseases (11, 12). To the best of our knowledge, this was the first study to investigate the prognostic significance of the CAR in a patient group with high mortality, such as CVID.

CVID is a heterogeneous group of antibody deficiencies characterized by low serum levels of immunoglobulin and an increased incidence of infection. Although CVID patients improve with regular IGRT, mortality and life-threatening morbidity rates remain high (13). Delays in diagnosis and inadequate treatment lead to increased irreversible complications and mortality (14). Resnick et al. reported that mortality in CVID patients was higher than in the general population (5). This was related to factors such as sex, age at diagnosis, complications (infectious and non-infectious), and baseline immunoglobulin levels. The study's mortality rate was 19.6% in 40 years of follow-up. Quinti et al. reported a mortality of 19.5%, a median age of death of 54, and a primary cause of death of chronic lung disease (30%) (15). In our study, the 12-year mortality rate was 20%, consistent with the literature. The most common cause of death was pneumonia and pneumonia-related sepsis (46.6%). The second most common cause of death was malignancies (33.3%).

Lymphoma is the most common malignancy in CVID, with a mortality rate of 8.2% in the USA, 3.8% in the UK, 3% in the ESID cohort, 2% in a Danish-Swedish cohort, and 1.8% in an Italian cohort (16). In our study, lymphoma developed in eight (10.6%) cases, and five (6.6%) patients died. These studies indicate an increased risk for malignancy, particularly lymphoma, in CVID, and this risk increases with age. Therefore, early diagnosis and definitive malignancy management can help CVID patients survive.

Previous studies have identified different cut-off values for predicting mortality. The cut-off value was 0.189 in Sun et al. (17) and 0.5 in Xu et al. (12). In our study, it was 2.1. The cut-off values differ because the studies used different units. The reference value for albumin was g/L in the above studies and g/dL in our research. In our study, with a reference value of g/L, the cut-off value is 0.21, which is close to the values in the literature. The 2.1 cut-off value in our study can be used to predict mortality due to its high specificity.

In a previous study, the clinical and immunological status of 248 CVID patients was evaluated. There was a relative deficiency of CD4 T cells (less than 400 cu/mm) in 20% of subjects (6). Further examination of this patient group revealed more opportunistic and severe infections. In addition, decreased peripheral B lymphocyte values were associated with reduced survival in CVID. In our study, $CD3^+$ T cells and $CD4^+$ T cells were significantly lower in CVID patients

who died than in surviving CVID patients (p = 0.002, p = 0.031, respectively). No significant differences were observed in $CD19^+$ B cells, but the switched memory B cell was significantly lower in deceased CVID patients (p = 0.029).

Immune dysregulation is an important complication in CVID patients. Autoimmunity is the symptomatic form of immune dysregulation, and symptoms related to autoimmune complications occur in 25% of patients (18). Self-tolerance is impaired due to the presence of autoreactive B and T cells. Congenital and acquired immune disorders can lead to abnormal B cell clones and the secretion of abnormal cytokines. The interplay of these issues leads to the coexistence of immunodeficiency and autoimmune conditions (19). CRP is an acute-phase reactant regulated by proinflammatory cytokines, particularly IL-6. CRP levels increase in the presence of a systemic inflammatory condition. On the other hand, albumin decreases because it is a negative phase reactant and due to a deteriorating nutritional status (9). In our study, high CRP, low albumin, and high CAR were independent risk factors for mortality.

The first limitation of this study is that it was retrospective and from a single center. The second limitation is that the patients' nutritional status was unknown when the CRP and albumin values were selected. Therefore, our results should be interpreted with caution and validated in future multicenter prospective studies.

In conclusion, infections and infection-related sepsis remain significant causes of death in CVID patients. Although survival rates are better in CVID patients than previously, mortality rates remain higher than in the general population. The CAR is simple, inexpensive, and an easily measurable parameter from routine clinical tests. Clinicians treating this patient group should consider a high CAR an independent risk factor for mortality and closely monitor these patients.

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Ethics

Ethics Committee Approval: The study was approved by Necmettin Erbakan University Noninterventional Clinical Research Ethical Committee (Decision no: 2023/4222, Date: 03.03.2023).

Informed Consent: The authors declared that getting consent from the patients was unnecessary because the study was a retrospective data analysis.

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