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The Prognostic Nutritional Index in Common Variable Immunodeficiency: A Marker for Mortality and Autoimmune Activity

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ABSTRACT

Objective: Common variable immunodeficiency (CVID) is the most prevalent symptomatic immunodeficiency in adults, involving various mutations and clinical presentations. Prognostic markers are not well-defined; however, non-infectious complications, especially autoimmunity, can impact survival and require personalized treatment. This study evaluates the potential of the prognostic nutritional index (PNI)—a marker for disease activity and prognosis in rheumatologic and malignant diseases—to indicate mortality and autoimmune status in CVID patients, along with its associations with demographic characteristics.

Materials and Methods: CVID patients followed at the Immunology Clinic between 2012 and 2024 were included, excluding those with advanced liver failure, active lymphoma, or severe lymphocytosis (>5000/mm^3). Age, diagnosis age, follow-up duration, initial immunoglobulin levels, mortality, and non-infectious complications were recorded, along with initial and current PNI values, albumin, and lymphocyte counts.

Results: The 72 patients had a median age of 35.5 years (IQR, 26.5–48.5); 33 were female (45.8%). Twelve patients (16.7%) died during follow-up. Autoimmunity was present in 32 patients (44.4%), splenomegaly in 30 (41.7%), malignancy in 6 (8.3%), and bronchiectasis in 28 (38.9%). Initial PNI value was associated with mortality, with a cutoff of <48.9 determined for mortality prediction, while current PNI values were also associated with mortality. Patients below this threshold had significantly higher mortality rates. Those with autoimmunity showed lower survival rates, along with reduced lymphocyte counts and current PNI levels. Initial PNI was positively correlated with pre-treatment IgG. In univariate survival analysis, older age, lower initial albumin and PNI values, and malignancy were linked to decreased survival.

Conclusion: Given the impracticality of categorizing CVID patients by infection frequency or non-infectious conditions for separate prognostic markers, PNI may serve as an affordable, easily monitored prognostic tool in CVID. Repeated PNI measurements could also provide insights into chronic inflammatory status, particularly in monitoring the development or activity of autoimmune complications.

Keywords: Common variable immunodeficiency, prognostic nutritional index, noninfectious complications, autoimmunity, mortality

INTRODUCTION

Although primary immunodeficiencies are considered rare diseases, increasing awareness and advances in technical capabilities have led to the realization that they are not as rare as once thought. To date, nearly 500 different mutations have been identified as causes of various immunodeficiency conditions (1). Among adults, the most common primary immunodeficiency, following selective IgA deficiency, is common variable immunodeficiency (CVID), which can be viewed as a diagnostic category encompassing numerous mutations and diverse clinical presentations (2). The reason patients are grouped into this common category is that CVID is characterized by an

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antibody production disorder. According to the criteria proposed by the European Society for Immunodeficiencies (ESID), the diagnosis of CVID should be accompanied by frequent infections or non-infectious immunological pathologies, inadequate vaccine antibody responses, and a significant decrease in serum IgG, accompanied by low IgA and/or IgM concentrations, demonstrated by repeated measurements (3). It is estimated that 1 in every 25,000 individuals has CVID (4). While there is no clear data regarding prognosis, it has been observed that survival rates are significantly higher in patients with infection-related complications compared to those with non-infectious complications, such as organ involvement (primarily in the lungs and gastrointestinal system) or the development of lymphoma (5,6). Non-infectious complications, particularly autoimmunity, play a significant role and are characterized by increased inflammatory burden in patients (7). Autoimmunity may be present at the time of diagnosis or may develop during follow-up (8). There is no clear parameter regarding which complications, including autoimmunity, may be observed in newly diagnosed CVID patients or how the prognosis may unfold. Several studies have linked parameters such as low serum IgG levels, elevated IgM, and decreased circulating B cell counts to increased mortality (5,9). Additionally, there are studies focused on variables that could predict which non-infectious complications a patient may be predisposed to (6,10). These prognostic and phenotypic marker studies aim to identify inflammatory variations or organ involvement early, with the goal of initiating appropriate treatments promptly to improve survival. However, there is no established parameter that is routinely recommended for use at diagnosis or during regular follow-up to predict the prognostic status of the disease or to forecast the presence or severity of non-infectious comorbidities, such as autoimmunity, that may exist or develop in the future.

The Prognostic Nutritional Index (PNI) is an immuno-nutritional screening index calculated using serum albumin and lymphocyte concentrations (11). Albumin, synthesized by hepatocytes, serves as an indicator of nutritional status and is also an acute-phase response protein with antioxidant and anti-inflammatory properties. In intense inflammatory processes, its circulating levels decrease due to increased catabolism and anabolic resistance. Studies indicate that low lymphocyte counts, one of the markers in PNI, can reflect disease progression, immunoparalysis, or nutritional status in various populations (12-14). The combined use of these two parameters has been shown to serve as a prognostic predictor in both preoperative patients and in non-surgical conditions such as rheumatological, cardiovascular, or malignancy-related diseases (11,15,16). However, to our knowledge, there is no study yet regarding the use of PNI as a prognostic or inflammatory marker in patients with existing immunodeficiency. The aim of this study was to assess the value of PNI in indicating mortality and autoimmune status in CVID patients and its relationship with patients' demographic characteristics.

MATERIALS and METHODS

This study included patients with CVID followed at the Immunology Clinic of Necmettin Erbakan University Faculty of Medicine between January 2012 and September 2024. The CVID diagnosis was determined according to the criteria proposed by ESID (3). Patients with advanced liver failure, active lymphoma, or severe lymphocytosis (over 5000/mm^3) in the context of lymphoproliferative disorders were excluded from the study. The most recent values for patients, who attended outpatient follow-up appointments for immunoglobulin replacement therapy at regular intervals (every 21 or 30 days for intravenous therapy, and every three months for subcutaneous therapy), were considered. Values recorded during hospitalizations, intensive care unit admissions, or unscheduled visits were not included. The patients' age, gender, age at diagnosis, follow-up duration, comorbidities, and current autoimmune status were documented. The Prognostic Nutritional Index (PNI) was calculated using the formula: 10 × serum albumin concentration (g/dL) + 0.005 × peripheral lymphocyte count (/mm^3). This study was approved by the Clinical Research Ethics Committee of Necmettin Erbakan University (decision no: 2024/5319) and was conducted in accordance with the principles of the Helsinki Declaration. Personal data of the patients were anonymized.

The statistical analysis of the research data was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using visual (histogram plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Since the continuous variables did not follow a normal distribution, the Mann-Whitney U test was used to evaluate the relationships between these variables, such as age, age at diagnosis, follow-up/survival duration, initial immunoglobulins, initial and current/last PNI, albumin, and lymphocyte

levels, as well as variability in PNI, based on mortality and presence of autoimmunity. Spearman's correlation test was used to assess the correlation between numerical variables. To determine the optimal PNI values for predicting mortality, a ROC curve analysis was performed considering both sensitivity and specificity. Univariate and multivariate survival analyses were conducted using the Cox model. Survival analyses based on categorized PNI values according to the mortality cut-off and the presence/absence of autoimmunity were performed (Kaplan-Meier). A significance level of $p<0.05$ was accepted for this study.

RESULTS

A total of 82 patients were evaluated for the study. Ten patients were excluded, including 3 with active lymphoma, 3 with severe lymphocytosis and lymphoproliferation, 3 with advanced liver failure, and 1 who had undergone liver transplantation.

Demographic Data and PNI

The median age of the 72 patients included in the study was 35.5 years (IQR, 26.5–48.5), with 33 females (45.8%). During follow-up, 12 patients (16.7%) died. The median initial and current PNI values of the 72 patients were 51.8 (IQR, 48.4–56.5) and 53.2 (IQR, 47.7–56.7), respectively. Autoimmune conditions were present in 32 patients (44.4%), with 12 patients having multiple autoimmune conditions concurrently (22 with cytopenia, 28 with thyroiditis, 2 with inflammatory bowel disease, and 1 each with autoimmune hepatitis, rheumatoid arthritis, alopecia, lupus, multiple sclerosis, and nephritis). In addition to autoimmunity, 30 patients (41.7%) had splenomegaly, 6 patients (8.3%) had malignancy, and 28 patients (38.9%) had bronchiectasis.

Spearman correlation tests revealed that age was negatively correlated with initial PNI. Initial PNI was positively correlated with initial IgG levels. Positive correlations were also found between current PNI and IgG as well as between IgM and IgG levels (Table I).

Mortality and PNI

The initial median PNI values measured at the time of diagnosis and the current median PNI values in patients who died were significantly lower than those in surviving patients (43.3 vs. 53.1, $p<0.001$ and 32.1 vs. 54.95, $p<0.001$, Table II). A significant difference was observed in the initial median albumin values constituting the initial PNI between deceased and surviving patients ($p<0.001$), while no significant difference was found in the median lymphocyte counts between the groups ($p=0.38$). The median values of both current albumin and lymphocyte counts showed significant differences between the groups ($p<0.001$ for both tests).

Table I: Correlation Table between Demographic Quantitative Data and PNI Values

Correlations									
			Age	**Diagnosis Age**	**Initial PNI**	**Current PNI**	**IgG**	**IgM**	**IgA**
Spearman's rho	Age	Correlation Coefficient							
		Sig. (2-tailed)							
	Diagnosis Age	Correlation Coefficient	0.929**						
		Sig. (2-tailed)	**0.000**						
	Initial PNI	Correlation Coefficient	-0.310**	-0.195					
		Sig. (2-tailed)	**0.010**	0.109					
	Current PNI	Correlation Coefficient	-0.190	-0.169	0.616**				
		Sig. (2-tailed)	0.111	0.163	**0.000**				
	IgG	Correlation Coefficient	-0.295*	-0.209	0.277*	0.265*			
		Sig. (2-tailed)	**0.013**	0.087	**0.022**	**0.026**			
	IgM	Correlation Coefficient	-0.118	-0.108	0.011	0.042	0.360**		
		Sig. (2-tailed)	0.330	0.379	0.927	0.730	**0.002**		
	IgA	Correlation Coefficient	-0.053	-0.041	0.074	0.103	0.477**	0.428**	
		Sig. (2-tailed)	0.667	0.744	0.552	0.401	**0.000**	**0.000**	

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Table II: Comparison of Demographic, Clinical Parameters, and PNI in Deceased vs. Surviving CVID Patients

	Death (n = 12)	Alive (n=60)	p-value
Gender (female), n (%)	4 (33.3)	28 (46.6)	0.10
Age (current), years	46 (35-60)	34 (25-44)	**0.033**
Age at diagnosis, years	38 (26.7-53.5)	25 (18-40)	0.051
Diagnosis duration, years	7 (5-9.7)	6 (4-11)	0.58
Bronchiectasis, n (%)	6 (50)	22 (36.6)	0.41
Malignancy, n (%)	4 (33.3)	3 (5)	**0.029**
Splenomegaly, n (%)	6 (50)	23 (38.3)	0.21
*Autoimmunity, n (%) -Cytopenias -Thyroiditis	8 (66) 6 (50) 7 (58)	24 (40) 16 (26.6) 21 (35)	0.08 0.1 0.11
IgG, g/L	2.57 (0.33–3.71)	3.1 (1.5-4.5)	0.052
IgM, g/L	0.3 (0.12–3.99)	0.42 (0.06–5.68)	0.51
IgA, g/L	0.23 (0.06–1.61)	0.26 (0.06–3)	0.59
Initial Albumin (g/L)	37.5 (30.5-41.5)	44 (41-46)	**<0.001**
Initial Lymphocyte (cell/mL)	1.65 (0.8-2.35)	1.7 (1.3-2.7)	0.38
Initial PNI	43.3 (39.1-47.4)	53.1 (50-56.9)	**<0.001**
Current Albumin (g/L)	25.4 (20.8-30.2)	45 (43.3-47.9)	**<0.001**
Current Lymphocyte (cell/mL)	0.51 (0.31-1.5)	1.8 (1.3-2.2)	**<0.001**
Current PNI	32.1 (24.1-36.1)	54.7 (51.4-57.3)	**<0.001**
PNI difference	-10.3 ((-16.6)- (-6.7))	-0.15 ((-2.4)-(4.1))	**<0.001**

Rheumatoid arthritis, lupus, Sjögren's syndrome, multiple sclerosis, nephritis, and autoimmune hepatitis diagnoses were observed in only one patient each and were therefore excluded from statistical analysis. The Chi-square test was used for frequency comparisons of categorical variables between groups, and the Mann-Whitney U test was applied for comparisons of numerical variables. Bold values indicate p-values <0.05. PNI difference = Current PNI - Initial PNI.

ROC analysis was used to determine the cut-off value based on initial PNI values for mortality. The cut-off value was 48.9, with sensitivity and specificity values of 0.83 and 0.17, respectively (Figure 1). Survival analysis performed by categorizing patients according to the cut-off value revealed significantly higher mortality in patients with PNI values below the threshold at the time of diagnosis (χ^2=16.9, log-rank p<0.001, Figure 2).

Effects of Non-Infectious Complications on Survival and PNI

According to the Cox proportional hazards model, the age at diagnosis, presence of cancer, initial albumin levels, and initial PNI were found to have a significant effect on survival in univariate analysis. However, no significant findings were observed in the multivariate analysis (Table III). Among the non-infectious complications, the presence of bronchiectasis, splenomegaly, autoimmunity, autoimmune cytopenia, or thyroiditis at the time of diagnosis did not have a significant effect on survival. However, according to the Kaplan-Meier survival analysis, the presence of autoimmunity was borderline significantly associated with mortality (χ^2=3.8, log rank=0.05, Figure 3).

The presence of autoimmunity was significantly associated with the lymphocyte count at diagnosis, current lymphocyte count, current albumin levels, current PNI, and the change in PNI (current PNI-initial PNI, Table IV).

DISCUSSION

In the present study, both the PNI values at the time of diagnosis and the current values were found to be associated with mortality in patients with CVID. A significant decrease in PNI values was also observed, and this decline was identified as an important marker of mortality. In patients with autoimmunity, the survival rate was found to

Table III. 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	1.06	1.01–1.08	**0.003**	1.028	0.98–1.07	0.16
Bronchiectasis	1.26	0.43–3.67	0.663			
Malignancy	0.29	0.09–0.94	**0.039**	1.00	0.14–6.99	0.994
Splenomegaly	0.59	0.21–1.65	0.321			
Autoimmunity	0.319	0.94-1.07	0.66			
IgG	0.97	0.74–1.27	0.870			
IgM	1.19	0.84–1.68	0.315			
IgA,	0.56	0.17–1.84	0.346			
Initial Lymphocyte	0.80	0.40-1.60	0.538			
Initial Albumin	0.15	0.07–0.31	**<0.001**	0.97	0.81–1.17	0.82
Initial PNI	0.79	0.71–0.89	**<0.001**	0.83	0.68–1.02	0.08

PNI: Prognostic Nutritional Index

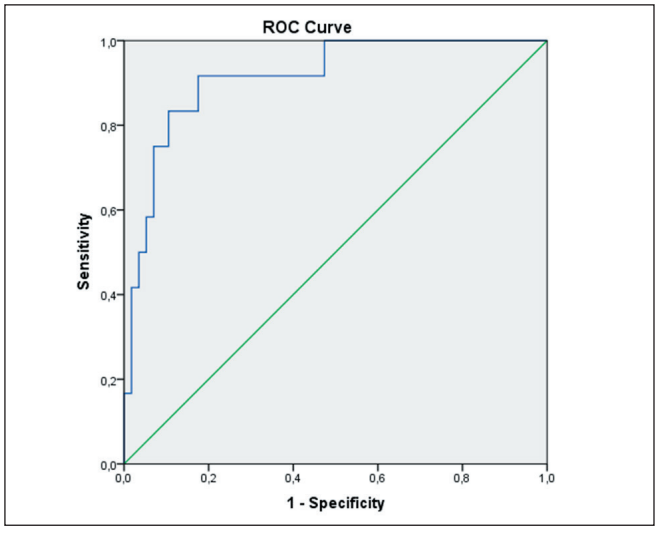

Figure 1. Receiver-operating characteristic (ROC) curve demonstrating the discriminative power of the Prognostic Nutritional Index (PNI) for predicting mortality. ROC analysis identified an optimal PNI cut-off of 48.9, the highest combined sensitivity (83%) and specificity (17%) intersected the curve. The area under the curve (AUC) was 0.914 (95% confidence interval [CI]: 0.672–0.903; p<0.001).

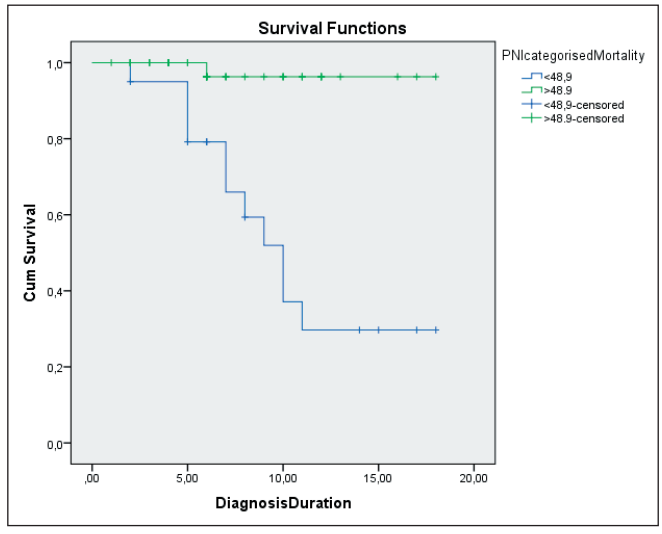

Figure 2. Overall survival stratified according to the Prognostic Nutrition Index (cut-off value 48.9) using the Kaplan-Meier method. (log rank<0.001).

be lower compared to those without autoimmunity. There was no difference between patients with and without autoimmunity in terms of the initial PNI; however, differences were observed in the current PNI and the change in PNI. Additionally, patients with autoimmunity had lower values of both initial and current lymphocyte counts compared to those without autoimmunity. The PNI values at diagnosis showed a positive correlation with IgG levels at diagnosis. In univariate survival analysis, higher age, lower initial albumin, and lower initial PNI were associated with survival, while among non-infectious complications, only the presence of malignancy was observed to have a negative impact on survival. These significant differences disappeared in multivariate analyses.

Table IV: Comparison of Demographic and Clinical Parameters, Including PNI, Based on Presence of Autoimmunity

	Autoimmunity present (n=32)	Autoimmunity absent (n=40)	p-value
Gender (female), n (%)	14 (43.7)	19 (47.5)	0.46
Age (current), years	35 (24-55)	38 (27-45)	0.79
Age at diagnosis, years	32 (17-49)	29 (19-39)	0.99
Diagnosis duration, years	6 (4-9)	6 (3.5-11)	0.58
Bronchiectasis, n (%)	14 (43.7)	14 (35)	0.30
Malignancy, n (%)	5 (15.6)	1 (2.5)	0.057
Splenomegaly, n (%)	13 (40.6)	17 (42.5)	0.53
Mortality, n (%)	8 (25)	4 (10)	0.08
IgG, g/L	3.7 (1.6–5.3)	2.7 (1.7-5.7)	0.59
IgM, g/L	0.35 (0.18–0.76)	0.19 (0.18–0.53)	0.07
IgA, g/L	0.26 (0.06–0.83)	0.25 (0.14–0.25)	0.52
Initial Albumin (g/L)	42.5 (40-46)	43 (40.5-45.1)	0.60
Initial Lymphocyte (cell/mL)	1.5 (0.7-2.1)	1.7 (1.4-2.7)	**0.038**
Initial PNI	51.7 (47.5-53.6)	52 (49.1-56.9)	0.43
Current Albumin (g/L)	43.7 (33-45.4)	45 (42.7-48)	**0.011**
Current Lymphocyte (cell/mL)	1.14 (0.51-2.04)	1.9 (1.5-2.7)	**0.01**
Current PNI	50.8 (35.6-55)	55.3 (51.5-57.6)	**0.02**
PNI difference	-2.8 ((-12.8)- (1.4))	-0.55 ((-4.)-(5))	**0.02**

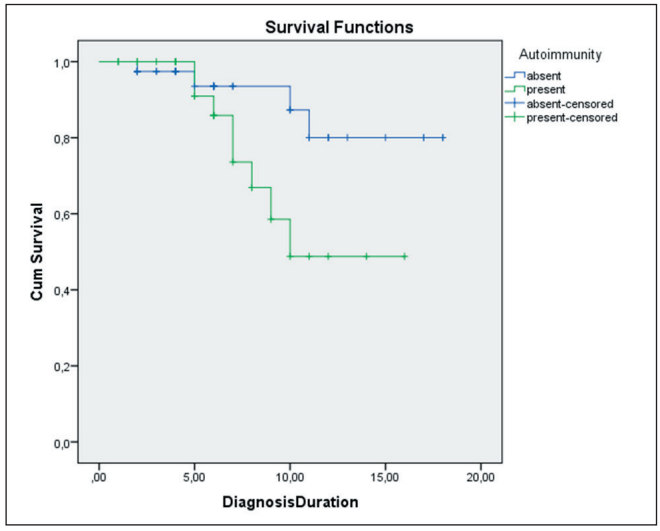

Figure 3. Kaplan-Meier survival curves for overall survival were divided into two groups according to the presence of autoimmunity. (log rank = 0.05).

CVID is a disease group characterized by a defect in humoral immunity, primarily involving B cells, and is marked by impaired antibody production (6). B cells may be numerically affected in CVID, as they constitute a small proportion of the total lymphocyte count; therefore, a significant decrease in the total lymphocyte count is not expected. The majority of circulating lymphocytes consist of CD4+ helper and CD8+ cytotoxic T cells. The diagnostic criteria for CVID require that T cell counts remain normal to differentiate these patients from those with combined immunodeficiency, in which T cell involvement is present (17). However, it is now recognized that the number of T cells in CVID patients can also be affected (18,19). This phenomenon has been particularly observed in adult-onset CVID cases (20). A specific example of this condition is the Late-Onset Combined Immune Deficiency (LOCID) subgroup of CVID, where a normal lymphocyte count at diagnosis later decreases over time (21). In general prognostic studies of CVID patients, those with T-cell abnormalities and lymphopenia tend to display a severe phenotype characterized by increased susceptibility to autoimmunity, and granuloma formation (22,23). In line with these observational studies, our findings show that patients with autoimmunity had significantly lower baseline lymphocyte counts compared to those without autoimmunity. In follow-up, the group with autoimmunity showed a more pronounced decline in PNI values, leading to a significant difference in current PNI values. This condition likely arises from both a decrease in albu-

min due to chronic inflammatory processes and the reduction in lymphocytes present from the onset. However, the presence of autoimmunity did not result in any difference in initial PNI values, as patients could receive a diagnosis with non-infectious complications such as autoimmunity, and autoimmunity can either emerge years after the initial CVID diagnosis or progressively worsen over time. Regarding mortality, the lower baseline PNI levels observed in deceased patients appear to stem from differences in albumin levels; however, the difference in current PNI levels is due not only to albumin but also to a significant reduction in lymphocyte levels. In summary, initial albumin values impact the reduced PNI levels in terms of mortality, whereas baseline lymphocyte levels are lower in those with autoimmunity. Over the follow-up period, declines in both parameters contribute to the reduction in current PNI. Thus, evaluating patients solely based on lymphocyte levels may not yield definitive results for assessing mortality or chronic inflammatory processes. The inclusion of albumin in the PNI score, given its substantial contribution to reflecting nutritional and inflammatory status, makes PNI a more advantageous indicator for monitoring both mortality and chronic inflammation compared to assessing each parameter individually. For this reason, recent studies have shown that PNI can be used not only to indicate prognosis but also to monitor the activity of primary autoimmune diseases and cancers (24,25).

Using ROC analysis, the PNI cut-off value established for predicting mortality shows high sensitivity but low specificity. This indicates that PNI values below the threshold at the time of diagnosis are highly effective in identifying patients with high mortality risk; however, patients who may have longer survival might also fall below this threshold. This outcome may not be entirely unexpected, given that CVID is a heterogeneous disease capable of affecting various organs—such as the liver, lungs, intestines, and endocrine glands—at different times through autoimmune, granulomatous, infectious, malignant, or mutation-specific complex histopathological patterns. Mortality in CVID can also result from infectious or non-infectious causes. Therefore, since this study demonstrated that a decrease in PNI values observed at regular intervals in follow-up negatively impacts survival, the false-positive results observed from a single measurement could be reduced by repeated assessments.

In the correlation tests, a noteworthy result is the correlation between the initial PNI and IgG. This finding may be attributed to a decrease in the number and activity of neonatal Fc receptors (FcRn), which prevent the random phagocytosis of albumin and IgG by circulating phagocytic cells, in patients with CVID. Circulating FcRn receptors bind to IgG and albumin via a pH-dependent mechanism, allowing them to be internalized by phagocytes. However, they do not undergo lysosomal degradation in the phagosomes, and instead, they are recycled back into circulation, where separation occurs again through a pH-dependent process (26). This binding and separation process occurs not only in circulation for IgG but also in the lumens of pathogen-exposed organs such as the lungs and intestinal system, where a significant amount of FcRn is secreted into the lumen (27). It has been concluded that a decline in these critical rescuing molecules occurs due to bronchial destruction or entheropathy, which is frequently associated with infections and autoimmune conditions in both CVID patients and animal models. Due to the same reason, CVID patients with bronchiectasis experience challenges in achieving target trough IgG levels with immunoglobulin replacement therapy compared to those without bronchiectasis, necessitating higher doses (28,29).

One of the other notable results in the correlation tests is the correlation between current age and initial PNI. Another finding is the negative correlation between IgG measured at the time of diagnosis and current age. Due to the fact that these results were observed with unrelated parameters across different time periods, they are considered to be coincidental. The lack of correlation between the PNI measured at the time of diagnosis and the age at diagnosis, as well as the lack of correlation between current PNI and current age, suggests that PNI is an age-independent parameter.

In the study, the patient group with severe lymphocytosis (greater than 5000/mm^3) was excluded from the analysis. In the PNI formulation, the lymphocyte count is multiplied by five and added to the albumin levels. Therefore, it is inevitable that patients with severe lymphocytosis have very high PNI levels, and as lymphocytosis progresses, the PNI increases further. This will distinctly differentiate this group from the other patients. The CVID phenotype associated with lymphoproliferation and lymphocytosis represents a challenging phenotype, as it involves lymphoid infiltration of vital organs, a condition for which treatment remains unresolved. Additionally, this group is at significantly increased risk for lymphoma development (30).

The limitations of the study include being conducted at a single center with a relatively small sample size and using a retrospective design. These factors have influenced some of the results. For example, while the presence of autoimmunity led to a significant difference in survival in the Kaplan-Meier survival analysis, no such difference was observed in the univariate survival analysis. Another example is the correlation between IgG and initial PNI, where the correlation test shows a significant relationship, and the initial PNI is notably lower in deceased patients. However, according to the Cox model, IgG remained non-significant in the univariate analysis (p=0.052). According to a large CVID study by Rasnic and colleagues, low IgG levels have been associated with reduced survival (5). Prospective studies involving a larger number of CVID patients are necessary to clarify the findings.

In conclusion, considering that categorizing CVID patients based on infection frequency, organ involvement, or complex immunological parameters is not feasible for daily practice, the PNI, as an inexpensive and easy to monitor parameter, can be used as a valuable prognostic tool in CVID except for the severe lymphocytosis-associated lymphoproliferative phenotype. In terms of the development of autoimmunity, which is the main non-infectious complication, or the activity of pre-existing autoimmunity, changes in PNI measurements taken at regular intervals may serve as a useful indicator for clinicians regarding the patient's chronic inflammatory status.

Conflict of Interest

The authors have no conflict of interests to declare.

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Author Contributions

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