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Original Article

Determinants of recurrence in ITP treatment

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Abstract: Objective: Immune thrombocytopenia (ITP) is the most common cause of thrombocytopenia. Two-thirds of the cases respond to first-line therapy with corticosteroids. However, there is a 50% relapse rate six months after the treatment. Information predicting recurrence at the time of the diagnosis is limited. This study aimed to investigate the relationship of mean platelet volume (MPV) and the neutrophil/lymphocyte ratio (NLR) at the time of the diagnosis with ITP recurrence. Methods: The study included 171 adult primary ITP patients who received corticosteroids and/or intravenous immunoglobulin (IVIG) as first-line therapy. The relationship between the demographic characteristics of the patients and the laboratory values at the time of the diagnosis with the frequency of recurrence was evaluated. Results: A total of 126 (73.7%) female and 45 (26.3%) male patients with a mean age of 38.54±17.41 years were included in the study. 89 (52%) patients had a recurrence after first-line therapy. No relationship was found between the frequency of recurrence and age, gender, the presence of comorbid diseases, bleeding status, type of the first-line treatment, CRP, and MPV values. However, there was a statistically significant relationship between NLR increase and the frequency of recurrence (P=0.049). Conclusion: In this study, an association was found between the NLR levels and the rate of recurrence in ITP patients receiving first-line treatment. Further studies with larger sample sizes are needed to support this finding.

Keywords: Immune thrombocytopenia, recurrence frequency, mean platelet volume, neutrophil-lymphocyte ratio

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by low platelet count and increased risk of bleeding. The estimated incidence is 100 cases per 1 million people per year, and approximately half of these cases are children [1].

The pathophysiology of ITP is not well understood; it has been tried to explain with various mechanisms including autoantibodies and cytotoxic T cells targeting platelets and/or megakaryocytes [2]. There is no diagnostic test for ITP. However, antiplatelet autoantibodies can be detected on the platelet surface in 40-60% of the patients [3]. Its diagnosis is based on the exclusion of other causes of thrombocytopenia [4].

ITP is categorized as primary or secondary depending on the presence of a reason causing immune thrombocytopenia. If there is a disease leading to immune thrombocytopenia, it is classified as “secondary ITP” or else “primary ITP” [5]. Corticosteroids are the standard initial treatment in primary ITP. Prednisone is the most commonly used drug, which is administered orally at a dose of 0.5-2 mg/kg daily. 65-70% of the patients respond to corticosteroids alone [6]. Nevertheless, complete long-term response with corticosteroids was reported in about 20% of the cases. Approximately 50% of the patients have a relapse within the first 6 months, and the disease recurs in 25% of the remaining patients within a year [7]. There is limited information to estimate the risk of recurrence at the time of the diagnosis. Studies are showing decreased risk of recurrence after Helicobacter pylori treatment, indicating age as a potential risk factor, and demonstrating the association of mean thrombocyte volume and risk of recurrence [8-10].

This study aimed to investigate the relationship between mean platelet volume (MPV) and the neutrophil/lymphocyte ratio (NLR) at the time of the diagnosis with the recurrence of ITP.

Table 1. Participant features

Patient characteristics		n	%
Sex	Female	126	73.7
	Male	45	26.3
Bleeding scale	No bleeding	27	15.8
	Petechia	85	49.7
	Mild blood loss	43	25.1
	Gross blood loss	15	8.8
	Debilitating blood loss	1	0.6
Medication history	No	137	80.1
	Yes	34	19.9
Comorbidity	None	134	78.4
	Hypertension	3	1.8
	Diabetes	4	2.3
	Hypothyroidism	6	3.5
	CAD	1	0.6
	Malignity	1	0.6
	Neurologic disease	2	1.2
	Rheumatologic disease	3	1.8
	Liver disease	2	1.2
	Multiple comorbidities	15	8.8

CAD: Coronary artery disease.

Materials and methods

Study design

A total of 171 patients with primary ITP diagnosed at adult-age during 2010-2018 and followed for at least one year after the diagnosis were enrolled in this retrospective study. Children, secondary ITP, patients not receiving treatment, patients without complete blood count at the time of diagnosis, and those with infection in the diagnosis were excluded from the study. Demographic data and laboratory values at the time of the diagnosis were determined. NLR was calculated by dividing neutrophil count by lymphocyte count.

Patients with a platelet count of >100,000/mm^3 after the treatment were considered to have a complete response, those with a rate of 30-100,000/mm^3 were accepted to have a partial response, and those with <30,000/mm^3 were considered as unresponsive.

Recurrence was defined as platelet counts less than 100,000/mm^3 in patients with complete response and less than <30,000/mm^3 in patients with a partial response, confirmed by at least two measurements. Statistical comparisons were made between the frequency of recurrence and demographic data, as well as laboratory values at the time of diagnosis. Ethical approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of the Van Yüzüncü Yıl University (Date: 12.10.2018, number: 06).

Statistical methods

The data were analyzed using the SPSS 25.0 software. The results were presented as frequencies, percentages, means, and standard deviations (SD). The Kolmogorov-Smirnov test was performed to test if the numerical variables were normally distributed. Most numerical variables were right-skewed, except for hemoglobin and MCV, which were left-skewed. The Mann-Whitney *U* test was used for skewed variables, and the Chi-square test (or Fisher's exact test) was used for categorical variables. A receiver operating characteristic (ROC) analysis was performed to check for sensitivity and specificity of NLR in predicting ITP recurrence.

Results

Participants

Results for 171 participants were analyzed. The mean age of the patients was 38.54± 17.41 years (range: 16-92 years). Most of the participants (73.7%; n=126) were females. According to the bleeding scale, most participants (49.7%; n=85) had petechia. Only 19.9% (n=34) had a medication history. The majority of the participants (78.4%; n=134) had no comorbidities. Detailed descriptions of the participants are given in **Table 1**.

Descriptive data

Descriptive serum levels of measured variables are presented in **Table 2**.

Outcome data

The most commonly employed first-line treatment was Prednol 1 mg/kg (71.9%; n=123), followed by Prednol 1 mg/kg + IVIG (28.1%; n=48), IVIG (2.9%; n=5), and high dose dexamethasone + IVIG (0.6%; n=1). Many participants (42.1%; n=72) showed a full response to treatment, while 9.4% (n=16) had a partial response and 28.1% (n=48) had no response.

Table 2. Serum levels of the numerical variables analyzed

Laboratory results	Median	95% CI for Median		Min.	Max.
		Lower	Upper		
Leucocyte count	8200	7800	8900	2600	14200
Neutrophil count	5400	5200	6000	1000	12300
Lymphocyte count	1900	1900	2100	700	4000
NLR	2.96	2.53	3.33	0.58	41.00
Hemoglobin	13.6	13.2	14.1	8.0	19.0
MCV	83	82	85	47	98
Thrombocyte count	8000	7000	11000	1000	89000
MPV	9.55	9.20	9.80	3.00	73.30
CRP	3.40	3.30	5.00	0.30	98.00
Creatinine	0.68	0.65	0.71	0.30	76.00
ALT	18	17	20	6	225
B12	266	249	290	83	849
Folic acid	6.3	5.7	7.3	2.2	19.7

NLR: neutrophil/lymphocyte ratio, MCV: mean corpuscular volüme, MPV: mean platelet volume, CRP: C-Reactive Protein, ALT: alanine aminotransferase, B12: vitamin B12.

On the other hand, 20.5% (n=35) of the patients became steroid dependent. The recurrence rate of the disease was 52.0% (n=89).

The recurrence rate did not differ significantly when compared against the type of the first-line treatment, sex, bleeding scale, medication history, or presence of comorbidity (**Table 3**). Among the studied variables, only NLR was significantly different in the patients with recurrence compared to patients without recurrence (**Table 4**). Age, leukocyte count, hemoglobin, MCV, platelet count, MPV, B12, folic acid, CRP, creatinine and ALT were not associated with recurrence.

The ROC analysis demonstrated an area under the curve (AUC) of 0.588 (**Figure 1**). A cut-off value of 2.06 for NLR was able to predict recurrence rate with a sensitivity and specificity of 77.5% and 43.2%, respectively (likelihood ratio-LR=1.37).

Discussion

Hundred and seventy-one primary ITP patients who received first-line treatment were examined in this retrospective study. Similar to the literature, recurrence rates were 52%. There was no relationship between age, sex, first-line treatment received, bleeding status, comorbid diseases, CRP, and MPV. Only NLR was associated with recurrence.

About half of the ITP cases are seen in children. In a study, it was found that childhood ITP was more common among boys [11]. In a study conducted in adults, the average age of ITP was 56, and the female/male ratio was 1.7. However, the incidence of men and women over age 60 was similar [1]. In our study, the mean age of the patients was 38.54 years, and the female/male ratio was 2.8. Besides, when we re-analyzed the patients over 60 years of age comparing sex distribution, in contrast to the literature, we observed a female/male ratio of 2.1, still demonstrating a female dominance.

The mean platelet volume is an indicator of platelet activation [12]. MPV has been shown to have a potential to be used for the diagnosis and differential diagnosis of ITP [13-15]. In a study, MPV (cutoff point 9.35 fl) was higher in ITP patients compared to myelodysplastic syndrome and healthy controls [13]. In a study comparing MPV values in patients with aplastic anemia (AA) and ITP at the time of diagnosis, it was shown that MPV was significantly higher in ITP (10.94±1.33) than AA (9.64±1.02) [16]. In a study evaluating MPV in the differential diagnosis of ITP and hyporeductive thrombocytopenia, MPV measured in ITP patients (11.38±0.57) was significantly higher than MPV measured in patients with hyporeductive thrombocytopenia (7.17±0.54) [17].

Additionally, the relationship between the recurrence of ITP and MPV was investigated in several studies [10, 18, 19]. One of these studies demonstrated a non-linear relationship between the MPV values at the time of diagnosis and the recurrence rate of ITP in 233 recently-diagnosed ITP patients. The risk of relapse increased linearly with MPV values up to 21 fl, while it abolished with values higher than 21 fl. As a result, the increase in MPV values up to 21 fl was shown to be an independent risk factor for the recurrence of ITP [10]. In another related study, MPV<8 fl was regarded as an independent prognostic indicator for permanent complete remission [18]. In our study, the mean MPV values were 9.25 fl and 9.80 fl in the remission and the relapse groups, respectively.

Table 3. Effects of different studied variables on the recurrence status

Patient characteristics		Recurrence status				χ^2 *and p-value*
		No recurrence		Recurrence		
		n	%	n	%	χ^2; *P*
Sex	Female	61	74.4	65	73.0	0.041; 0.841
	Male	21	25.6	24	27.0	
Treatment	Prednol 1 mg/kg	57	69.5	66	74.2	3.346; 0.287*
	High dose dexamethasone	0	0.0	0	0.0	
	IVIG	1	1.2	4	4.5	
	Prednol 1 mg/kg + IVIG	23	28.0	19	21.3	
	High dose dexamethasone + IVIG	1	1.2	0	0.0	
Bleeding scale	No bleeding	9	11.0	18	20.2	5.611; 0.230
	Petechia	42	51.2	43	48.3	
	Mild blood loss	20	24.4	23	25.8	
	Gross blood loss	10	12.2	5	5.6	
	Debilitating blood loss	1	1.2	0	0.0	
Medication history	No	68	82.9	69	77.5	0.781; 0.377
	Yes	14	17.1	20	22.5	
Comorbidity	None	67	81.7	67	75.3	4.522; 0.970
	Hypertension	2	2.4	1	1.1	
	Diabetes	1	1.2	3	3.4	
	Hypothyroidism	3	3.7	3	3.4	
	CAD	0	0.0	1	1.1	
	Malignity	0	0.0	1	1.1	
	Neurologic disease	1	1.2	1	1.1	
	Rheumatologic disease	1	1.2	2	2.2	
	Liver disease	1	1.2	1	1.1	
	Multiple comorbidities	6	7.3	9	10.1	

*Fisher's exact test, IVIG: intravenous immunoglobulin, CAD: Coronary artery disease.

Table 4. The relationship of the studied mean blood values with the recurrence status

Laboratory results	Recurrence status										*Z*	*P*
	No recurrence					Recurrence						
	Median	95% CI		Max.	Min.	Median	95% CI		Max.	Min.		
		Lower	Upper				Lower	Upper				
Age	34	30	36	92	16	32	29	46	81	17	-0.164	0.870
Leucocyte count	8000	7500	8900	29200	2600	8500	7700	9200	23400	3300	-1.045	0.296
Neutrophil count	5350	4200	5900	26300	1000	5700	5200	6400	18900	1800	-1.707	0.088
Lymphocyte count	1900	1800	2100	6000	700	1800	1500	2100	5200	300	-0.156	0.876
NLR	2.56	2.00	3.14	29.22	0.58	3.31	2.73	3.65	41.00	0.97	-1.972	0.049
Hemoglobin	13.6	13.2	14.1	18.1	5.2	13.1	12.4	14.0	19.0	8.0	-1.517	0.129
MCV	84	83	85	96	47	82	81	85	98	53	-0.874	0.382
Thrombocyte count	7500	6000	10000	72000	1000	9000	8000	15000	89000	1000	-1.200	0.230
MPV	9.25	8.70	9.70	73.30	5.00	9.80	9.50	10.20	13.70	3.00	-1.745	0.081
CRP	3.40	3.30	6.70	98.00	0.30	3.40	3.30	5.60	57.00	2.90	-0.433	0.665
Creatinine	0.69	0.64	0.74	76.00	0.50	0.68	0.64	0.72	1.46	0.30	-1.209	0.227
ALT	19	17	25	225	6	17	15	19	142	6	-1.305	0.192
B12	273	248	302	849	83	264	232	299	802	144	-0.704	0.481
Folic acid	5.9	4.7	7.2	19.7	2.2	7.0	5.8	9.1	18.9	2.8	-1.679	0.093

NLR: neutrophil/lymphocyte ratio, MCV: mean corpuscular volüme, MPV: mean platelet volume CRP: C-Reactive Protein, ALT: alanine aminotransferase, B12: vitamin B12.

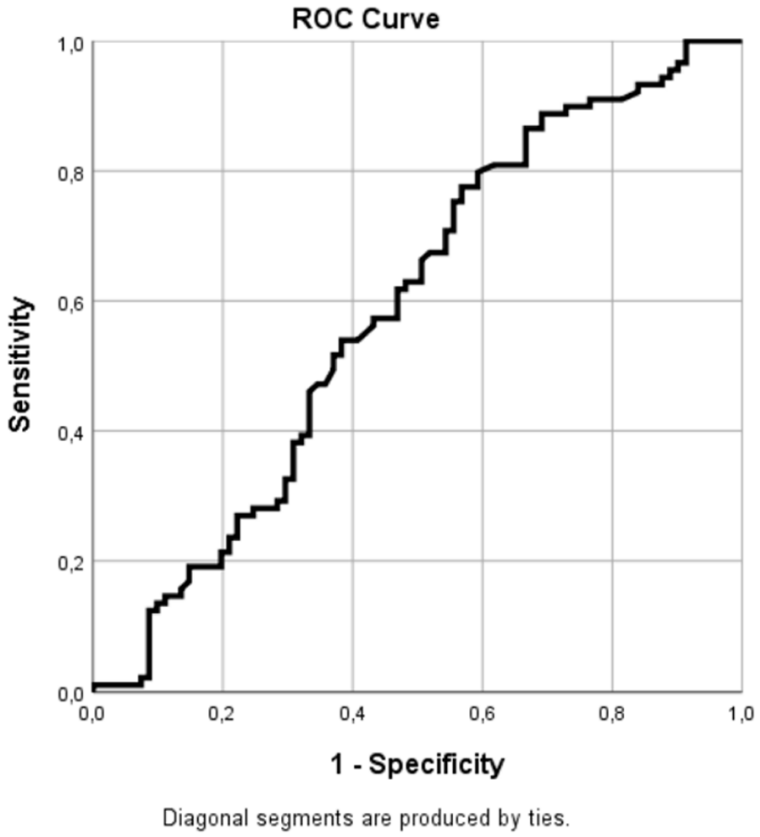

Figure 1. ROC curve analysis for NLR.

The difference between the two groups was not statistically significant (P=0.081).

The neutrophil/lymphocyte ratio has been found to be a new potential determinant of systemic inflammation in various diseases such as coronary heart disease, sarcoidosis, psoriasis, chronic kidney disease, and malignancy [20-24]. Furthermore, it has been suggested that high levels of NLR are associated with poor prognosis in some diseases [21, 24-26]. In this study, elevation in the NLR levels was associated with ITP recurrence (P=0.049). As to the receiver operating characteristics (ROC) analysis, the cut-off value for NLR was 2.06 with a sensitivity of 77.5% and a specificity of 43.2%.

This study has several limitations. The retrospective nature of the research together with the non-standard follow-up periods of the patients and the presence of multiple first-line treatments have to be considered when interpreting our results.

Conclusion

In conclusion, we still do not have enough data to predict recurrence in ITP patients. In this study, we determined the NLR ratio as a potential predictor for recurrence. We found a relationship between increases in the NLR levels and relapse-rates. However, due to the low sensitivity and specificity of our NLR cut off value, we need more prospective studies to claim the clinical application of NLR as an indicator.

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The study was approved by the Van Yüzüncü Yıl University Local Ethics Committee (protocol number: 12.10.2018/06).

Disclosure of conflict of interest

None.

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