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Comparing Neutrophil-to-lymphocyte Ratio, Platelet-to-lymphocyte Ratio, and Hemoglobin-to-platelet Ratio Between Patients With Immune Thrombocytopenia and Healthy Controls: A Retrospective Study

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ABSTRACT

Background: Immune thrombocytopenia (ITP), formerly known as idiopathic thrombocytopenic purpura, is a common hematologic disorder that affects a wide range of people but is more prevalent in children and older people. Evaluation and measurement of inflammatory markers in patients with ITP are costly and time-consuming. Considering the importance of inflammation in ITP, the reduction of blood cells, and the occurrence of thrombocytopenia and anemia, the use of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and hemoglobin-to-platelet ratio (HPR) indices can be effective in ITP management due to their relevance to clinical symptoms, low cost, and availability. Therefore, we investigated these indices in this study.

Materials and Methods: This is a retrospective, descriptive, and epidemiological study conducted at Ahvaz Jundishapur University of Medical Sciences, Baqaei Hospital, Ahvaz City, Iran, in 2020 and 2021. In this study, 250 ITP patients comprised the case group, and 70 healthy individuals comprised the control group.

Results: The results showed that the mean PLR was lower in patients (1.29±2.24) than in controls (69.88±33.01), while the mean NLR (2.146±2.16 vs 0.966±0.919) and HPR (0.752±0.707 vs 0.049±0.017) in patients were significantly higher than in healthy individuals (P=0.0001). On the other hand, there was no significant difference between the mean corpuscular volume (MCV) (P=0.584) and white blood cell (WBC) (P=0.943) indices between the two groups. To evaluate the diagnostic value of PLR, NLR, and HPR indices, receiver operating characteristic (ROC) curves were used, and area under the curve (AUC) values were calculated. The AUC for NLR was about 71%, while for PLR and HPR it was 100% and 98%, respectively.

Conclusion: In general, PLR, NLR, and HPR indices have diagnostic and prognostic value in the management of ITP.

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Introduction

Immune thrombocytopenia (ITP), formerly known as idiopathic thrombocytopenic purpura, is a common hematologic disorder that affects a wide range of people but is more prevalent in children and older people [1]. The disease is divided into two categories: Primary and secondary. The primary type is characterized by isolated thrombocytopenia (platelet count<100×10^9) and an increased risk of bleeding in the absence of other causes of thrombocytopenia. In contrast, the secondary type occurs in the context of immunological diseases or infections [2]. In terms of clinical symptoms, people with ITP also have symptoms such as bleeding, thrombosis, and fatigue [3]. The etiology of thrombocytopenia lies in the production of antibodies against glycoproteins (GPIIb/IIIa and GPIb/Ix) on the surface of platelets and megakaryocytes, which are removed from the blood by the reticuloendothelial system due to their antibody sensitivity, leading to a decrease in platelet count [4]. Recent studies have shown that inflammatory processes are closely related to the pathogenesis of this disease, and serological evaluations indicate increased levels of inflammatory cytokines, such as interleukin (IL)18 (from the IL1 family), in these individuals. Recent evidence suggests that immune system dysfunction, driven by environmental and genetic factors, plays an important role in the progression of the disease. Immune system dysfunction results from either acquired or inherited immune systems, which involve innate immune cells and B and T lymphocytes [5]. Therefore, evaluating these biomarkers is important for diagnosing and monitoring people with the disease [6]. Evaluation and measurement of these cytokines and inflammatory markers in patients with ITP are costly and time-consuming. It is also not very economical to conduct experiments in developing and low-income countries because of their high costs. Therefore, by introducing new markers and cases where their measurement is low-cost and readily available, patients at high risk of developing inflammatory ITP can be identified.

Platelet-to-neutrophil ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are among the cheap, fast, and available inflammatory indices. In addition to indicating inflammation, these indices can be used to assess patient prognosis and survival, so that increases in these indices indicate decreased survival and a poor prognosis [7, 8]. A study by Wang et al. evaluating PLR and glucocorticoid resistance in ITP patients found a non-linear relationship between PLR levels and glucocorticoid resistance [9]. Given the importance of inflammation in ITP, the reduction in blood cells, and the occurrence of thrombocytopenia and anemia, the use of PLR, NLR, and Hb-to-platelet ratio (HPR) indices can be effective in ITP management due to their relevance to clinical symptoms, low cost, and availability. Therefore, we investigated these ratios in this study.

Materials and Methods

This retrospective, descriptive, and epidemiological study was conducted at Ahvaz Jundishapur University of Medical Sciences, Baqaei Hospital, Ahvaz City, Iran, in 2020 and 2021. The study participants were ITP patients referred to the hospital's Oncology Ward. All patients had their ITP disease confirmed by an oncologist before enrollment based on clinical and laboratory examinations. Diagnoses of ITP were made according to the criteria of the American Society of Hematology. The inclusion criteria included patients without underlying disease and those with no history of thrombocytopenia. The exclusion criteria included patients with thrombocytopenia (human immunodeficiency virus [HIV]) infection, myeloproliferative disorders, and SLE). In this study, a data collection form was prepared. The collected data included patients' demographic information (age, sex), clinical symptoms, treatment type, and hematological parameters. Cell percentages were used to calculate PLR, NLR, and HPR indices. Informed consent was obtained from all patients before participating in the study.

The thrombocytopenia was confirmed by bone marrow biopsy, and all patients with primary ITP were included in the study—this screen-based information was in their clinical file.

Data analysis

Mean and median were used to describe the data. Quantitative data were also shown as percentages. The chi-square test was used to analyze qualitative data. Quantitative data were also used for data analysis, and for this purpose, we used the t test for quality data analysis. Receiver operating characteristic (ROC) curves were used to assess the diagnostic value of the indices. All analyses were performed using SPSS software, version 23. In this study, a $P<0.05$ was considered significant.

Results

Demographic and clinical information of the patients

In this study, 250 ITP patients participated as the case group, and 70 healthy individuals as the control group. The results showed that the mean age was nearly identical in both groups. Therefore, no significant relationship was observed between them. Also, in the control group, 41.1% were women and 58.6% were men, whereas in the case group, 54% were women and 46% were men. Table 1 presents the prevalence of clinical symptoms and the type of treatment.

Table 1. Demographic information of the study participants

Variables		Mean±SD/No. (%)		P
		Control (n=70)	Case (n=250)	
Age (y)		10.39±15.09	10.02±11.27	0.210
Sex	Female	29(41.4)	100(40)	0.056
	Male	41(58.6)	150(60)	
Manifestation	Fever	-	Yes 86(34.4)	-
			No 164(65.6)	
	Purpura	-	Yes 106(42.4)	-
			No 144(57.6)	
	Petechiae	-	Yes 102(40.8)	-
			No 148(59.2)	
	Bruise	-	Yes 120(48)	-
			No 130(52)	
	Ecchymosis	-	Yes 50(20)	-
			No 200(80)	
	Bleeding	-	Yes 96(38.4)	-
			No 154(61.6)	
	Cold	-	Yes 122(48.8)	-
			No 128(51.2)	
	Petechiae, purpura, and ecchymosis	-	Yes 83(33.2)	-
			No 167(66.8)	
	Petechiae, purpura	-	Yes 80(32)	-
			No 170(68)	
	Ecchymosis, petechiae	-	Yes 67(26.8)	
			No 183(73.2)	
	Epitaxy and ecchymosis	-	Yes 89(35.6)	-
			No 161(64.4)	
	Petechiae and bruise	-	Yes 69(27.6)	-
			No 181(72.4)	
	Bleeding and bruising	-	Yes 58(23.2)	-
			No 192(76.8)	
	Fever and cold	-	Yes 4(1.6)	-
			No 182(98.4)	

Variables		Mean±SD/No. (%)		P
		Control (n=70)	Case (n=250)	
Manifestation	Petechiae, purpura, and cold	-	Yes 61(24.4)	-
			No 189(75.6)	
	Ecchymosis and cold	-	Yes 72(28.8)	-
			No 178(71.2)	
Drug	Prednisolone and IVIg		230(92)	-
	Prednisolone, IVIg, and corton		18(7.2)	-
	IVIg and corton		2(0.8)	-

Table 2. Comparing blood indexes between groups

Postoperative Blood Results and Hematological Parameters	Mean±SD		P
	Control	Case	
Hemoglobin (g/dL)	12.87±1.9	11.14±1.66	0.0001
Hematocrit	38.12±4.16	34.31±6.85	0.0001
MCV (fL)	78.93±7.12	78.46±7.57	0.584
MCH (pg)	33.29±1.21	27.21±4.9	0.0001
Red blood cell ($\times 10^6$)	4.84±0.698	4.35±0.728	0.0001
White blood cell ($\times 10^3$)	9.34±3.6	9.59±4.2	0.943
Lymphocytes (%)	4.85±3.13	36.80±19.75	0.0001
PMN	3.31±1.53	49.85±23.25	0.0001
Platelet ($\times 10^3$)	277.64±63.65	36.8±47.58	0.0001
ANC	0.320±0.210	5.12±3.63	0.0001
ALC	0.547 ±0.922	3.65±2.523	0.0001
NLR	0.966±0.919	2.146±2.16	0.0001
PLR	69.88±33.01	1.29±2.24	0.0001
Hb/PLT	0.049±0.017	0.752±0.707	0.0001

Abbreviations: MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; ANC: Absolute neutrophil count; ALC: Absolute lymphocyte count; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; Hb/PLT: Hemoglobin-to-platelet ratio.

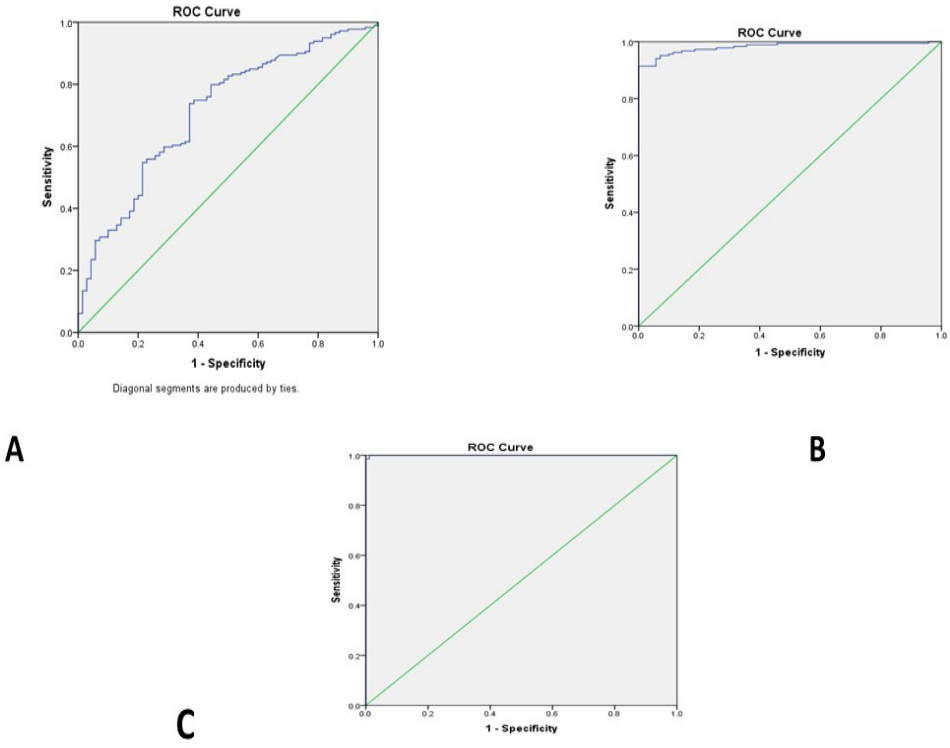

Figure 1. The ROC curves correspond to the diagnostic power of NLR (A), HB/PLT (B), and PLR (C)

Table 3. Explanation of the ROC analysis

Biomarker	AUC	Cutoff (approx.)	Sensitivity (%)	Specificity (%)	Youden's Index
NLR	0.713	2.8	52	66	0.66+0.52-1=0.18
HPR	0.982	10	50	96	0.96+0.50-1=0.46
PLR	1	115	76	79	0.79+0.76-1=0.55

Abbreviations: NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; Hb/PLT: Hemoglobin-to-platelet ratio.

Comparable blood parameters between groups

The results showed that the mean PLR was lower in patients than in controls, while the mean NLR and HPR in patients were significantly higher than in healthy individuals (P=0.0001). On the other hand, there was no significant difference in the mean corpuscular value (MCV) and white blood cell (WBC) indices between the two groups (Table 2).

Evaluation of HPR, PLR, and NLR as diagnostic factors

To evaluate the diagnostic value of PLR, NLR, and HPR indices, ROC curves were used, and area under the curve (AUC) values were calculated. The AUC for NLR was about 71%, while those for PLR and HPR were 100% and 98%, respectively (Table 3).

The AUC for NLR was about 71%, while those for PLR and HPR were 100% and 98%, respectively (Figure 1).

Discussion

The evaluation of inflammatory markers and their monitoring are important for diagnosing many diseases. Diseases that can be identified using inflammatory markers include appendicitis, arthritis, multiple myeloma, irritable bowel syndrome, Crohn's disease, and multiple sclerosis. One challenge in diagnosing ITP is reliance on laboratory criteria. A set of clinical symptoms and laboratory criteria primarily defines the disease. An important laboratory marker recently discussed in the context of ITP is the inflammatory index. Numerous inflammatory indices have been identified to date, but a significant challenge in their use is their availability and cost-effec-

tiveness. These available, cost-effective inflammatory indices include PLR, NLR, and the HPR ratio.

A study by Qin et al found that the NLR and PLR increased in patients with systemic lupus erythematosus (SLE). Increased levels of these indices are associated with elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and indicate inflammation in these patients. Finally, in the above study, it was concluded that NLR and PLR levels reflect the inflammatory response and disease activity in patients with SLE [10]. In a meta-analysis by Hao et al., the NLR was strongly associated with Bechet's disease (BD), rheumatoid arthritis (RA), and ankylosing spondylitis. PLR levels also increase in patients with SLE and RA. In general, the researchers in this study recommended using PLR and NLR markers as cost-effective biomarkers for diagnosing inflammatory and autoimmune diseases [11]. Also, in the study of Zhang et al. it was concluded that the ratios of hemoglobin, neutrophils, and lymphocytes have diagnostic and prognostic value in patients with BD [12]. In a study by MO et al. the results showed that the use of PLR and HPR markers plays an important role in identifying inflammatory processes and diagnosing rectal cancer. Thus, increased PLR and HPR have been associated with increased carcinoembryonic antigen (CEA) tumor markers in patients with rectal cancer [13]. In another study, Arshad et al. showed that, similar to the present study, PLR and NLR levels decreased and increased in patients compared with the control group, respectively [14]. Ahmadi et al. also showed that, as in the present study, PLR levels were lower in patients than in the control group [15].

In addition, recent studies indicate that these markers play a diagnostic role in identifying inflammatory processes in patients with ITP. Therefore, in this study, the effects of PLR, NLR, and HPR markers on the diagnosis and prognosis of patients with ITP were evaluated. Findings of this study showed that the mean PLR in the ITP group was lower than in controls, while the mean NLR and HPR values in the ITP group were higher than in controls. All three inflammatory indices, PLR, NLR, and HPR, in patients with ITP were proportional to their clinical status and were statistically significant (P=0.0001) in such a way that they are very helpful in diagnosing the disease.

On the other hand, the results of the ROC chart, which relate to the role of these markers in diagnosing the disease and assessing patient prognostic status, have been different. This chart shows that PLR and HPR markers have higher diagnostic and prognostic value than NLR.

In contrast to the present study, Yang et al. found that the NLR ratio is appropriate for diagnosing patients with ITP, but its use to determine prognostic status requires further investigation. The reason for this difference in results is related to the statistical population and clinical status of patients. In the study by Yang et al., the subjects had a chronic clinical condition, in which case the inflammatory process is initiated. The main cells involved in this process are neutrophils, and this factor can help assess the effectiveness of the NLR index in diagnosis. Therefore, comparing these two studies, it can be said that chronic ITP disease can enhance the effectiveness of the NLR index. In other words, the use of the NLR marker indicates a chronic inflammatory condition in patients with ITP [16]. Also, the study by Eren et al. shows that the NLR index's power to predict patient response to corticosteroid treatment is very weak, and there is no significant relationship between response to NLR treatment in patients with ITP [17]. This study, like the present study, shows the limitations of the NLR marker in predicting patient prognosis. The study by Song et al. yielded a similar result to ours. In this study, the findings indicate a non-linear relationship between the PLR and disease recurrence in patients with ITP. The PLR marker can be used as a useful parameter to diagnose the disease and assess the prognostic status of patients [18]. Therefore, the use of PLR, NLR, and HPR markers, which are affordable and readily available, can help diagnose ITP and assess the prognostic status of patients with ITP.

It is important to note that the AUC obtained for PLR is 100%. Although this number is statistically significant, given the limited number of patients, it is better to conduct a larger study to evaluate the results further.

Conclusion

This study found that PLR, NLR, and HPR have diagnostic value in ITP patients. However, due to the limitations of this study, including its small patient sample and retrospective design, further investigation is needed.

Study limitations

The small number of patients, the retrospective design, and the use of a single treatment center were among the limitations of this study.

Future perspective

Suggestions for future studies include conducting prospective studies, using machine learning, and conducting multi-center studies.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Code: IR.AJUMS.REC.1400.627). Informed consent was obtained from all patients before participating in the study

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Authors contribution's

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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