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Original Article

# NLR, PLR, and HPR as novel diagnostic biomarkers for Acute Lymphoblastic Leukemia

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## Abstract

**Background:** Acute lymphoblastic leukemia (ALL) causes uncontrolled cell proliferation and prevents normal cell differentiation at any stage of hematopoiesis. Therefore, timely diagnosis and treatment is very important. Complete blood count (CBC) can be a simple, but valuable initial test to diagnose ALL. In this study, we investigated the diagnostic value of hematological parameters, including Platelet to lymphocyte ratio (PLR), neutrophil-to lymphocyte ratio (NLR), and hemoglobin to Platelet ratio (HPR) indices in ALL.

**Methods:** In this study, 54 ALL patients (Mean ages: 5.29) and 58 healthy controls (Mean ages: 5.53) were evaluated. They were compared in terms of hematological parameters, including PLR, NLR, and HPR; cytogenetic and immunophenotype were also analyzed.

**Result:** In the analysis of hematological factors between the studied groups, all indices except lymphocytes showed a statistically significant relationship (P-Value <0.05. In terms of hematological factors, only WBC and ESR were statistically significant between the B-ALL and T-ALL groups (P-Value <0.05). The ROC curve was generated to select the appropriate cut-off values for NLR, PLR and HPR based on analysis. NLR and PLR have cut-off values of 0.50 and 62.24, respectively; they are good biomarkers to distinguish ALL individuals from normal people. HPR value was significant between case and control groups, but it was not a suitable indicator for distinguishing patients from the control group.

**Conclusion:** CBC is a simple and valuable test for early detection of ALL, and the new PLR and NLR markers are good hematologic markers for ALL diagnoses.

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## 1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood leukemia and the second most common childhood cancer in the world (1). The prevalence of this cancer is estimated at 1.6 per 100,000 people in the United States. In 2018 about 5960 new cases were diagnosed (2).

Genetic mutations in ALL, in addition, to disrupting the proliferation and differentiation of B lymphocytes, can also affect T type. Together, these changes increase

the number of immature inflammatory cells in the blood, leading to symptoms (3). Considering the fact, that ALL is an aggressive malignancy, and one of the common causes of death in children, early diagnosis is very important; it leads starting treatment. Diagnosis time directly affects treatment and consequently prognosis. So, effective communication between the clinic and laboratory is required to elevate the quality of diagnosis and treatment. Looking for the onset of symptoms in children with ALL, a Complete blood count (CBC) is one of the first tests requested; its interpretation provides important information for ALL monitoring (4).

In recent years, much attention has been paid to the link between inflammation and cancer (5). Antitumor activity occurs during inflammation; in fact, the activity of the immune system causes tumor growth, inflammation, human cancer progression and carcinogenesis. Inflammatory cells and their products are important regulators of tumor microenvironment (6). Therefore, carcinogenesis is associated with chronic inflammation (7).

CBC is especially important because of its convenience and cheapness. In CBC, values such as: White blood cell (WBC), neutrophil, platelet, lymphocyte and mean platelet volume are analyzed. The obtained information can be used as inflammatory markers. Neutrophils act as a major component of the immune system. Other cells, such as platelet and lymphocytes, have been shown to be effective in inflammatory processes (8-10). In general, a separate examination of cited markers can show early inflammation. PLR, NLRand HPRare common clinical parameters of inflammation before treatment; they are associated with an unfavorable prognosis of several malignancies (11-13). These markers can be used as diagnostic or prognostic markers. To date, no study has examined the diagnostic value of NLR, PLR and HPR indices in ALL. Therefore, in this study we investigated the diagnostic value of these indices.

## 2. Method

### 2.1. Patients and sample

This retrospective study was conducted in Cancer Molecular Pathology Research Center of Mashhad University of Medical Sciences. All studied patients had referred to our center, and were diagnosed with ALL during October 2019-July 2020. In our study, 54 children with ALL and 58 normal children participated as control population. Patients with ALL were selected based on WHO 2018 classification and were divided into B-All and T-All groups by performing flowcytometry and examining CD markers. Also, patients were divided into subgroups L1, L2 and L3 based on FAB classification.

Peripheral blood and bone marrow smears were prepared for whole patients. Necessary molecular and cytogenetic tests were performed. Two pathologists or two hematologists examined peripheral blood and bone marrow smears, and diagnosed the disease based on the tests results. Finally, CBC was also prepared for patients by sysmex K Seri device, and then was confirmed by a hematopathologist. Patient's CBC was used to calculate inflammation-related indices.

### 2.2. Ethical issues

This study was approved by the ethics committee of Mashhad University of Medical Sciences. It was one of the articles extracted from the results of project number 960039, under the ethics code of IRMUMS. fm.RC.1396.276

### 2.3. Statistical analysis

Data was analyzed by IBM 25.0 software. Data distribution was determined using Shapiro - Wilk test, histogram and Q-Q diagrams. Chi-square test was used to analyze the categorical variable of patients in terms of number and percentage.

After drawing the receiver-operating characteristic (ROC) curve using the Youden index (J), the cut-off values for ALL detection and the area under the curve (AUC) were calculated. Confidence interval 95% was calculated, and two tailed p <0.05 was considered statistically significant.

## 3. Result

The final analysis was performed on 54 ALL patients and 58 healthy controls. The mean age in ALL and control group were 5.29 and 5.53, respectively. In the analysis of hematological factors between the two groups, all indices except lymphocytes showed a statistically significant relationship (P-Value <0.05) (**Table 1**).

Another analysis was performed on 54 ALL children. The mean age of B-ALL children, which were categorized based on the stage of disease were 9.20 and 4.43 for the Early and Late B ALL, respectively; The mean age of T-ALL group was 3.88, which was statistically significant (P-Value = 0.04) (**Table 2**). In terms of gender and type of ALL (L1, L2 and L3), no

significant relationship was observed between the two groups (P-Value >0 0.05) (**Table 2**).

Patients were evaluated for clinical signs and symptoms, such as fever, bone pain, lymphadenopathy, ecchymosis, epistaxis, fatigue, splenomegaly and mediastinal mass, but no significant relationship was observed between the two groups (P-Value = 0.142) (**Table 2**).

Cytogenetic analysis showed, 21.1% of B-Late and 20% of T-ALL patients had numerical chromosomal abnormalities. Cytogenetics even indicated that 33.3% of B-early patients and 5.3% of B-Late patients had structural abnormalities. Also, 33.3% of B-early patients, 5.3% of B-Late patients and 40% of T patients had complex chromosomal abnormalities. In this study we also found out that t (12:21) in 31.6% of B-early patients, and 36.8% of B-early patients. 33.3% of B-Late patients and 40% of the T-ALL patients had normal karyotype. There was no statistically significant relationship between the two groups (P-Value = 0.239) (**Table 2**).

Normal cytogenetic pattern is defined as the presence of 22 pairs of somatic chromosomes in association with XX or XY sexual chromosomes, without any structural abnormalities. Numerical cytogenetic abnormality is an abnormality in which the karyotype does not have the normal number of chromosomes (23 pairs of chromosomes).; It is less or more numbers of chromosome. Structural cytogenetic patterns are types of karyotypes with shifting fragments of chromosomes between different arms. Complex karyotype is also kind of pattern with more than one abnormality, either numerical or structural (14).

Immunophenotype examination of patients, demonstrated a statistically significant relationship between CD3, CD5, CD7, CD10, CD19, CD20 and CD33 markers (P-Value <0.05) (**Table 3**).

In terms of hematology indices, a significant relationship was observed between the two groups in WBC (P-Value = 0.032) and ESR (P-Value = 0.029) parameters. But other indices did not show any significant relationships (P-Value >0.05) (**Table 4**).

The ROC curve was depicted to select the appropriate cutoff values for NLR, PLR and HPR based on analysis (**Figure 1**). For NLR in B-ALL, the area under curve (AUC) was 0.75 (95% CI: 0.63-0.88, P-Value=0.000), and the sensitivity and specificity on the ROC curve were 68.33% and 57.31%, respectively (**Figure 1A**). For PLR, the AUC was 0.76 (95% CI: 0.63-0.88, P-Value=0.000), and sensitivity and specificity on the ROC curve were 64.78% and 60.13%, respectively (**Figure 1A**). For HPR the AUC was 0.67 (95% CI: 0.50-0.83, P-Value=0.027), and sensitivity and specificity on the ROC curve were also 43.07% and 80.94%, respectively (**Figure 1A**).

For NLR in T-ALL, the AUC was 0.73 (95% CI: 0.51-0.94, P-Value= 0.041), and sensitivity and specificity on the ROC curve were 50.29% and 53.06 %, respectively (**Figure 1B**). For PLR, the AUC was 0.86 (95% CI: 0.73-0.99, P-Value=0.001), and sensitivity and specificity on the ROC curve were also 61.22% and 65.98%, respectively (**Figure 1B**).

Totally for comparing of controls with ALL group for NLR, the AUC was 0.75 (95% CI: 0.63- 0.86, P-Value= 0.000), and sensitivity and specificity were 49.99% and 50.14 %, respectively (**Figure 1C**). For PLR, the AUC was 0.78 (95% CI: 0.67-0.89, P-Value=0.000), and sensitivity and specificity were 53.8% and 66.39%, respectively (**Figure 1C**). For HPR the AUC was 0.66 (95% CI: 0.54-0.79, P-Value=0.015), and sensitivity and specificity were also 37.79% and 86.58%, respectively (**Figure 1C**).

## 4. Discussion

Our study showed, pre-treatment biomarkers such as NLR, PLR and HPR can effectively predict ALL. NLR and PLR can also be specific biomarkers for predicting B-ALL and T-ALL. Although the prognostic role of NLR and Monocyte to lymphocyte ratio in large B cell lymphoma (DLBCL), Hodgkin's lymphoma and multiple myeloma has been well established, the diagnostic importance of biomarkers in ALL has not been reported (15). Feng and colleague evaluated CBC parameters as prognostic factors for 75 newly diagnosed T-cell lymphoblastic lymphoma. They reported, that NLR, PLR and lymphocyte to Monocyte ratio can be good predictor of overall survival (OS) and progression free survival (PFS) (16). As it was mentioned before, the prognostic significance of NLR and PLR in many diseases is studied. Wang et al. evaluated CBC markers for 182 patients with DLBCL. They indicated optimal cutoff values for high NLR (≥2.32) and PLR (≥150) in prognosis prediction; they also reported, that patients with high PLR and NLR had shorter OS and PFS (13). But, in the present study, the survival information of patients was not available.

The relationship between NLR and prognostic power is not yet well understood. Several studies have shown that activated neutrophils can inhibited T-cell by increasing arginase 1 (17). In addition to T-cell suppression, neutrophils

Table 1. Demographic and CBC data of participants

| Patients Characteristic | CASE | CONTROL | P-Value |
|---|---|---|---|
| Age (mean ±SD) | 5.29±3.42 | 5.53±2.82 | |
| Male | 22(40.7) | 24(40) | |
| Female | 32(59.3) | 34(60) | |
| Hemoglobin(g/dl)(mean±SD) | 8.92±3 | 13.98±1.24 | 0.0001 |
| Hematocrit (mean±SD) | 26.73±9.26 | 40.79±3.07 | 0.0001 |
| MCV(fl) (mean±SD) | 82.87±9.35 | 86.45±3.72 | 0.013 |
| MCH (pg) (mean±SD) | 27.52±4 | 29.81±1.5 | 0.0001 |
| MCHC (g/dl) (mean±SD) | 33.51±2.06 | 34.26±1.14 | 0.004 |
| Red blood cell ($\times 10^6$) | 3.22±1.18 | 4.72±0.42 | 0.0001 |
| White blood cell ($\times 10^3$) | 34.01±55.44 | 6.93±1.42 | 0.043 |
| Lymphocytes (%) | 45.7±25.97 | 36.47±7.36 | 0.186 |
| PMN | 18.28±17.31 | 51.1±9.61 | 0.0001 |
| Platelet ($\times 10^3$) | 133±137.59 | 258.6±45.52 | 0.0001 |
| ANC | 3.46±5 | 3.60±1.17 | 0.0001 |
| ALC | 15.51±43.62 | 2.41±0.55 | 0.003 |
| NLR | 0.641±1 | 1.49±0.5 | 0.0001 |
| PLR | 43.60±56.80 | 108.72±30.3 | 0.0001 |
| HPR | 0.191±0.271 | 0.056±0.012 | 0.015 |

MCV: mean corpuscle volume; MCH: Mean corpuscle hemoglobin; MCHC; Mean corpuscle hemoglobin concentration; PMN: polymorphonuclear leukocytes; ESR: erythrocyte sedimentation rate; ANC: Absolut neutrophile count; ALC: Absolut lymphocyte count; PLR: platelet to lymphocyte ratio; HPR: hemoglobin to platelet ratio.

Table 2. Patients Characteristics

| Patients Characteristics | B-ALL | | T-ALL | P Value |
|---|---|---|---|---|
| | Early | Late | T Precursor | |
| Age (mean±SD) | 9.20±5.6 | 4.43±2.38 | 3.88±1.69 | |
| Male | 0 (0) | 9 (39.1) | 3 (33.3) | |
| Female | 5 (100) | 14 (60.9) | 6 (66.7) | |
| L1 | 3 (60) | 19 (82.6) | 7 (77.8) | |
| L2 | 2 (40) | 4 (17.4) | 2 (22.2) | 0.538 |
| L3 | 0 (0) | 0 (0) | 0 (0) | |
| Manifestation | | | | |
| Fever | 2 (40) | 2 (10.5) | 1 (14.3) | |
| Bone Pain | 1 (20) | 3 (15.8) | 0 (0) | |
| Lymphadenopathy | 1 (20) | 2 (10.5) | 0 (0) | |
| Fever and bone pain | 1 (5.3) | 0 (0) | 0 (0) | 0.142 |
| Ecchymosis | 1 (5.3) | 0 (0) | 0 (0) | |
| Epistaxis | 1 (14.3) | 0 (0) | 1 (5.3) | |
| Fatigue | 0 (0) | 1 (20) | 7 (36.8) | |
| Splenomegaly | 2 (10.5) | 0 (0) | 2 (28.6) | |
| Mediastinal mass | 0 (0) | 0 (0) | 3 (42.9) | |
| Cytogenetic | | | | |
| Numerical | 0 (0) | 4 (21.1) | 1 (20) | |
| Structural | 1 (33.3) | 1 (5.3) | 0 (0) | 0.239 |
| Complex | 1 (33.3) | 1 (5.3) | 2 (40) | |
| t(12,21) | 6 (31.6) | 0 (0) | 0 (0) | |
| Normal | 7 (36.8) | 1 (33.3) | 2 (40) | |

Table 3. Immunophenotype of Patients

| Immunophenotype | B-ALL | | T-ALL | |
|---|---|---|---|---|
| | Early | Late | T Precursor | P Value |
| **CD2** | | | | |
| Negative | 0 (0) | 3 (100) | 0 (0) | 0.25 |
| Positive | 0 (0) | 0 (0) | 1 (100) | |
| **CD3** | | | | |
| Negative | 5 (100) | 22 (100) | 3 (42.9) | 0.0001 |
| Positive | 0 (0) | 0 (0) | 4 (57.1) | |
| **CD5** | | | | |
| Negative | 5 (100) | 18 (100) | 3 (33.3) | 0.0001 |
| Positive | 0 (0) | 0 (0) | 6 (66.7) | |
| **CD7** | | | | |
| Negative | 1 (100) | 7 (100) | 1 (16.7) | 0.006 |
| Positive | 0 (0) | 0 (0) | 5 (83.3) | |
| **CD34** | | | | |
| Negative | 1 (50) | 1 (14.3) | 1 (16.7) | 0.520 |
| Positive | 1 (50) | 6 (85.7) | 5 (83.3) | |
| **CD10** | | | | |
| Negative | 7 (77.8) | 1 (20) | 1 (4.5) | 0.0001 |
| Positive | 2 (22.2) | 4 (80) | 21 (95.5) | |
| **CD19** | | | | |
| Negative | 0 (0) | 1 (4.5) | 9 (100) | 0.0001 |
| Positive | 5 (100) | 21 (95.5) | 0 (0) | |
| **CD20** | | | | |
| Negative | 1 (25) | 3 (37.5) | 8 (100) | 0.011 |
| Positive | 3 (75) | 5 (62.5) | 0 (0) | |
| **CD33** | | | | |
| Negative | 3 (100) | 10 (100) | 7 (100) | 0.0001 |
| Positive | 0 (0) | 0 (0) | 0 (0) | |
| **CD117** | | | | |
| Negative | 3 (100) | 18 (94.7) | 9 (100) | 0.722 |
| Positive | 0 (0) | 1 (5.3) | 0 (0) | |
| **CD13** | | | | |
| Negative | 3 (100) | 10 (91) | 4 (100) | 0.689 |
| Positive | 0 (0) | 1 (9) | 0 (0) | |

can contribute to tumor microenvironment by angiogenesis processes, and increase tumor metastasis by matrix metalloproteinase expression (18). Beltrán et al. evaluated NLR for 121 patients as a marker for PFS and OS. They asserted, that NLR ≥6 was associated with lower complete remission rate and lower 5-year PFS rate; while NLR <6 in patients was associated with better OS and PFS (19). In the study by Go et al. high NLR was related to worse OS and PFS, and generally to poor treatment response in DLBCL (20). Unfortunately, we did not have any information about patients' survival, and the prognostic significance has not been investigated in presented study. Actually, present study focused on the diagnostic value of CBC inflammatory indices, while many other published studies have focused on prognostic value as mentioned. In our study, NLR and PLR have the cut off value of 0.50 and 62.24, respectively; reducing these biomarkers can be a good factor for distinguishing ALL from normal people. Even, we evaluated the role of HPR biomarker for ALL diagnosis from normal individuals. Although HPR value was significantly different between the case and control groups, it was not a good biomarker for diagnosis of ALL from normal individuals. Dogan and associates examined the same indices for ALL individuals; the calculated

Table 4. **Hematological parameters of patients**

| Postoperative blood results and hematological parameters | B-ALL | | T-ALL | P-Value |
|---|---|---|---|---|
| | Early | Late | T Precursor | |
| Hemoglobin(g/dl)(mean±SD) | 8.180±3.51 | 8.66±2.93 | 10.77±3.42 | 0.369 |
| Hematocrit (mean±SD) | 24.68±10.61 | 26.30±9.56 | 32.24±9.06 | 0.270 |
| MCV(fl) (mean±SD) | 84.66±7.09 | 82.54±5.15 | 82.23±6.13 | 0.788 |
| MCH (pg) (mean±SD) | 27.84±2.83 | 28.23±8.72 | 26.916±1.93 | 0.912 |
| Red blood cell ($\times10^6$) | 2.88±1.20 | 3.106±1.102 | 3.96±1.29 | 0.180 |
| White blood cell ($\times10^3$) | 6.16±5.73 | 38.81±68.53 | 47.31±46.08 | **0.032** |
| Lymphocytes (%) | 56.80±28.13 | 44.13±23.75 | 44.25±27.53 | 0.698 |
| PMN | 21.60±18.20 | 17.27±18.91 | 18.50±13.91 | 0.447 |
| Platelet ($\times10^3$) | 79.20±69.41 | 144.818±148.96 | 125.222±108.8 | 0.822 |
| ESR | 125±0 | 79.08±43.59 | 44.86±40.99 | **0.029** |
| BLAST | 20.50 ±9.84 | 38.05±27.66 | 44.66 ±34.47 | 0.489 |
| LDH | 1899±1907.26 | 825.07±311.58 | 3236.71±2748.03 | 0.176 |
| Band cell | 5±0 | 2.857±5.475 | 0.40±.894 | 0.289 |
| Atypical Lymphocytes | 4.50±6.36 | 2.69±3.326 | 2.167±3.48 | 0.755 |
| Blast in aspiration | 80±14.14 | 76.66±8.164 | 80±0 | 0.848 |
| ANC | 1.362±1.69 | 3.481±4.246 | 5.839±8.812 | 0.270 |
| ALC | 3.498±3.141 | 20.78 ±62.26 | 10.30±7.146 | 0.200 |
| NLR | 0.6250±.6319 | 0.569±.758 | 1.077±2.198 | 0.812 |
| PLR | 37.045±31.87 | 45.56±63.147 | 24.05±38.06 | 0.406 |
| HPR | 0.1370±.0742 | 0.2354±.37152 | 0.132±.088 | 0.927 |

MCV: mean corpuscle volume; MCH: Mean corpuscle hemoglobin; MCHC; Mean corpuscle hemoglobin concentration; PMN: polymorphonuclear leukocytes; ESR: erythrocyte sedimentation rate; ANC: Absolut neutrophil count; ALC: Absolut lymphocyte count; PLR: platelet to lymphocyte ratio; HPR: hemoglobin to platelet ratio.

NLR and PLR had the diagnostic sensitivity of 49.9 and 53.8, respectively; (21). We also specifically examined NLR, PLR, and HPR for differentially detection of T-ALL and B-ALL from controls. The AUC for NLR and PLR was 76% and 75%; it indicated, that they are good indices for differentiating B-ALL from healthy individuals. Although HPR was a poor biomarker for the diagnosis of B-ALL, this biomarker could not detect the disease occurrence, well. We also evaluated the diagnostic value of NLR and PLR for T-ALL. Overall, we indicated, that PLR and NLR despite HPR are the best diagnostic biomarkers for T-ALL. The diagnostic role of HPR has been proven in colon cancer; recently, its prognostic importance has also been determined for hepatocellular carcinoma (22, 23). Simple, fast and available parameters are needed to diagnose and determine the prognosis of malignancies such as ALL, which rapidly progresses. Despite many progresses in the laboratory tests, nowadays many researches have evaluated independent and inflammatory parameters of CBC for leukemia diagnosis and prognosis determination(4). Usul and coworkers in turkey evaluated the diagnostic value of hematological parameters in COVID-19 infected individuals. The cut off point for NLR in COVID-19 infected individuals was ≤ 1.8; so, low NLR was introduced as a good prognostic marker for COVID-19 diagnosis (8). COVID-19 is an infectious disease that can be associated with decreased platelets, leukocytes and neutrophils. Fluctuations in blood cell counts during disease can act as a prognostic marker for disease. Zihan Jin studied the diagnostic value of NLR and PLR in rheumatoid arthritis (RA) patients. These two markers were higher in the RA group compared to the healthy individuals. Finally, they suggested NLR as a complementary test for RA diagnosis, but it was not as sensitive as C- reactive protein and rheumatoid factor (24). RA is an inflammatory disease, and the rate of inflammation is higher than ALL, so the difference

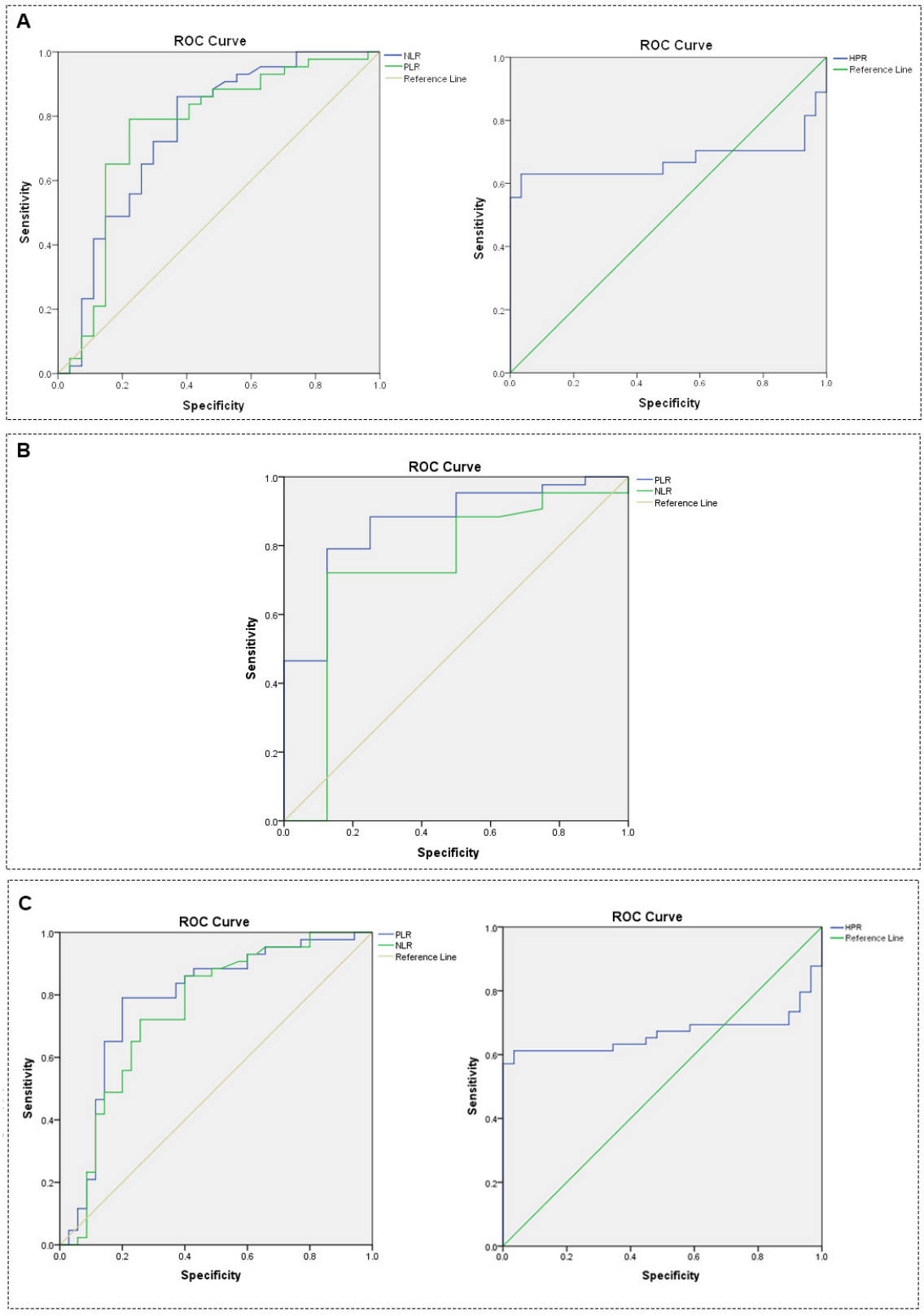


Figure 1. The ROC curve was depicted to select the appropriate cutoff values for NLR, PLR, and HPR. A) ROC curves of NLR, PLR and HPR for diagnosis of B-ALL. B) ROC curves of NLR, PLR and HPR for diagnosis of T-ALL. C) ROC curves of NLR, PLR and HPR for diagnosis of ALL.

between the amounts of inflammatory indices may be due to the disease identity.

Stojkovic also introduced NLR, PLR, and MPV as useful markers for colorectal cancer diagnosis; they were also good markers for recognition of various stages of colorectal cancer (25). CBC as simple, fast and inexpensive test is always requested for the first examination of many patients, but it has some limitations. It does not detect and count immature cells, especially blasts, which are very vital to leukemia diagnosis. Leukemia is usually diagnosed by bone marrow aspiration analysis and cytogenetic and molecular tests; but cytogenetic and molecular analysis are not available everywhere, and it leads to late diagnosis. Therefore, the use of CBC indices and their ratio to each other can detect ALL occurrence with acceptable sensitivity and specificity.

## 5. Conclusion

According to the results of the present study, NLR and PLR are relatively good indices for initial diagnosis of B-ALL and T-ALL unlike HPR; As a matter of fact, CBC is an economical test for the primary evaluation of patients. Physicians can use these new markers in combination with clinical signs for primary diagnosis. However, further studies with a larger statistical community can be helpful.

## Ethical approval

This study was approved by the ethics committee of Mashhad University of Medical Sciences. It was one of the articles extracted from the results of project number 960039, under the ethics code of IRMUMS. fm.RC.1396.276. .

## Conflict of interest

The authors declare no conflict of interest.

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## Data availability

All the data have been included in the manuscript and will be made available upon publication of the manuscript.

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