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The diagnostic value of inflammatory biomarkers in the diagnosis and treatment of influenza B in adults

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Abstract

Influenza can lead to various complications if not promptly diagnosed and treated. This study aims to assess the predictive value of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammation response index (SIRI), which are derived from routine blood parameters, in diagnosing influenza infection in adults. This study included 130 patients diagnosed with and treated for influenza B from 2022 to 2024. The control group comprised 130 healthy individuals. Influenza B diagnosis was confirmed using rapid antigen kits, and complete blood counts were analyzed *via* spectrophotometric/impedance methods, with statistical evaluation applied to the results. Among the 130 patients included, 55.3% (n=72) were male. Patients were categorized into two groups: those treated on an outpatient basis and those hospitalized. NLR, PLR, and SIRI values were significantly higher in hospitalized patients than in outpatients ($p<0.001$ for all parameters). In patients diagnosed with influenza B, NLR [6.11 (1.76-17.15)], PLR [266.66 (138.20-914.28)], and SIRI [3.56 (0.82-10.11)] values were significantly elevated compared to the control group [NLR 1.63 (0.45-2.22); PLR 99.21 (61.84-169.37); SIRI 0.73 (0.45-1.48)] ($p<0.001$ for all comparisons). The NLR threshold was set at 2.36, achieving 96.7% sensitivity and 100% specificity ($p<0.001$). The PLR threshold was 153.41 [area under the curve (AUC)=0.988, sensitivity: 93.3%, specificity: 92.9%, $p<0.001$], and the SIRI threshold was 1.36 (AUC=0.977, sensitivity: 93.1%, specificity: 92.9%, $p<0.001$), confirming the diagnostic relevance of these parameters. This study demonstrates that NLR, PLR, and SIRI, which are non-invasive, cost-effective, simple, and reproducible biomarkers, provide strong prognostic value in diagnosing and managing adult patients with influenza B, particularly in cases requiring hospitalization.

Key words: influenza B, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, systemic inflammation response index, nasopharyngeal swab.

Introduction

Influenza is an RNA virus from the Orthomyxoviridae family, with types A and B being particularly pathogenic to humans. Symptoms typically appear abruptly, and the disease is often self-limiting. Influenza infection is generally confined to the upper respiratory tract, presenting with symptoms like fever, sore throat, runny nose, cough, headache, myalgia, joint pain, fatigue, and malaise. In some cases, however, the infection may progress to life-threatening complications, including pneumonia, acute respiratory distress syndrome, and multi-organ failure due to secondary bacterial infections [1]. In the absence of early diagnosis and treatment, complications can also develop in non-respiratory systems [2].

While most influenza cases are diagnosed based on clinical symptoms, this virus may present with clinical profiles similar to those of other respiratory viruses, such as rhinovirus, respiratory syncytial virus (RSV), Covid-19, and parainfluenza. This similarity can make it challenging to distinguish influenza from other respiratory infections. Therefore, obtaining respiratory samples and performing thorough laboratory testing are essential for accurate diagnosis. The gold-standard laboratory methods for diagnosing influenza include viral culture, reverse transcription polymerase chain reaction (RT-PCR), and serological tests. However, viral culture and serological testing are often too time-consuming for use in outpatient settings. Although RT-PCR provides rapid results, it is costly and requires specialized equipment [3]. In recent years, low-cost rapid antigen tests have been developed, yet these tests have limitations, including a tendency toward false-negative results and low sensitivity [4]. To overcome these limitations, faster molecular assays with high specificity and sensitivity have been developed [5].

Ratios like neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR), and systemic inflammation response index (SIRI) have been widely used in various studies to evaluate malignancies, pulmonary thromboembolism, ischemic stroke, and rheumatologic and cardiovascular diseases [6,7]. Recently, these parameters have also shown potential as predictive markers in the early diagnosis of infectious diseases, including viral infections. Specifically, a single-center retrospective study demonstrated that NLR, PLR, and mean platelet volume/platelet ratio (MPV/PLT) are valuable prognostic markers for early diagnosis in children [8]. However, studies on influenza virus infections in adults remain limited [9]. In a study conducted between September 2020 and December 2020, 1,330 influenza A cases were compared with 1,330 healthy controls, showing that NLR, PLR, platelet count (PLT), and absolute lymphocyte counts were significantly elevated in influenza A cases ($p < 0.001$) [10]. Another study confirmed the prognostic significance of SIRI in cardiovascular diseases [11]. Given this context, our study aims to explore the predictive value of NLR, PLR, and SIRI, derived from routine blood parameters, in diagnosing influenza infection in adults.

Materials and Methods

This retrospective, single-center study was approved by the Ethics Committee for Clinical Research at Gazi University Faculty of Medicine (decision number 1153, dated 09.07.2024). A total of 178 patients diagnosed with influenza B between July 1, 2022, and July 1, 2024, were screened through our system for inclusion. Forty-eight patients who did not meet the study criteria were excluded, and 130 patients were selected for final analysis (Figure 1). The control group consisted of 130 healthy individuals. Patients aged 18 years and older who tested positive for influenza B through nasopharyngeal swab samples were included in the study. Patients with hematologic disorders, significant liver and kidney dysfunctions, a history of malignancy, pregnancy, or other viral infections (such as influenza A, coronavirus, RSV, adenovirus, and mycoplasma) were excluded. Demographic data (age, sex), smoking status, comorbidities, symptoms, respiratory support needs, antiviral and antibiotic treatments, and complete blood count values of the participants were recorded in patient follow-up forms. Complete blood counts were analyzed in our hospital laboratory using spectrophotometric/impedance methods (Beckman Coulter LH 780 Analyzer; Beckman Coulter, Inc., CA, USA). NLR was calculated as the ratio of neutrophil count to lymphocyte count, while PLR was calculated as the ratio of platelet count to lymphocyte count. SIRI was calculated using the following formula: (Neutrophil count × Monocyte count) / Lymphocyte count.

Nasopharyngeal swab samples were analyzed in our hospital's clinical microbiology laboratory using immunochromatographic rapid antigen kits. Swab samples were prepared in a reaction tube and evaluated according to the instructions provided by the kit manufacturer.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics for continuous variables were expressed as mean ± standard deviation and median (minimum-maximum), while categorical variables were expressed as number and percentage (%). The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test, and nonparametric tests were employed based on the results. Pearson's chi-square (χ^2) test was applied to categorical data, Student's t-test to normally distributed continuous data, and the Mann-Whitney U test to non-normally distributed data. The relationships between variables were assessed using Spearman's correlation coefficient. Cut-off points for NLR, PLR, and SIRI values were determined by Receiver Operating Characteristic (ROC) analysis. A significance level of $\alpha=0.05$ was set for all tests, and differences between groups were considered statistically significant at $p<0.05$.

Results

A total of 130 patients diagnosed with influenza B through nasopharyngeal swab samples were included in the study. The mean age of the study population was 53.36 ± 14.05 years, with 72 patients (55.3%) being male and 58 (44.6%) female. The duration of symptoms before admission ranged from 2 to 7 days, with a median duration of 4 days. Comorbidities were identified in 101 patients (77.7%), while 29 patients (22.3%) had no accompanying comorbidities.

Detailed demographic characteristics are presented in Table 1. During the course of treatment, 57 patients (43.8%) required hospitalization, with 51 (39.2%) admitted to the general ward for an average duration of 4.97 ± 2.83 days. Six patients (4.6%) required admission to the intensive care unit (ICU), with an average ICU stay of 8.2 ± 5.4 days.

The rate of complications among patients was 23.8% (n=31). Complications included viral pneumonia in 4.6% (n=6) and secondary bacterial pneumonia in 12.3% (n=16) as lower respiratory tract infections. Additionally, 5.4% (n=7) of patients required non-invasive mechanical ventilation, and 1.5% (n=2) required invasive mechanical ventilation.

Evaluation of the patients' blood parameters showed a median NLR value of 6.11 (1.76-17.15), a median PLR value of 266.66 (138.20-914.28), and a median SIRI value of 3.56 (0.82-10.11). When patients were divided into two groups—outpatients and those requiring hospitalization—the median NLR value for hospitalized patients was 8.61 (4.10-17.15), while it was 5.12 (1.76-6.68) for outpatients, a statistically significant difference ($p<0.001$). Similarly, the median PLR and SIRI values were also significantly higher in hospitalized patients compared to outpatients. For PLR, median values were 320.80 (157.51-914.28) in hospitalized patients and 230.05 (138.20-324.39) in outpatients; for SIRI, median values were 4.18 (2.12-10.11) and 2.31 (0.82-4.27), respectively ($p<0.001$ for both). Spearman's correlation analysis revealed positive correlations between hospitalization and NLR ($p<0.001$, $r=0.845$), PLR ($p<0.001$, $r=0.864$), and SIRI ($p<0.001$, $r=0.867$). The control group consisted of 130 healthy individuals with a mean age of 57.57 ± 15.68 years, of whom 81 (62.3%) were male. Comparisons of laboratory test results and measured values between the two groups are presented in Table 3. In patients diagnosed with influenza B, NLR, PLR, and SIRI values were significantly higher compared to the control group ($p<0.001$ for all) (Table 2).

ROC analysis was conducted to determine cut-off values for NLR, PLR, and SIRI in diagnosing influenza. The NLR threshold was determined to be 2.36, with a sensitivity of 96.7% and specificity of 100% ($p<0.001$) (Table 3, Figure 2). For PLR, the threshold was set at 153.41, with an AUC value of 0.988, sensitivity of 93.3%, and specificity of 92.9% ($p<0.001$) (Table 3, Figure 2). The SIRI threshold was 1.36, with an AUC of 0.977, sensitivity of 93.1%, and

specificity of 92.9% ($p<0.001$) (Table 3, Figure 3). These results indicate that NLR, PLR, and SIRI exhibit high accuracy and reliability in diagnosing influenza.

Discussion

Seasonal influenza virus causes an infection that emerges primarily in winter months and can spread epidemically [12]. Disease severity varies between years, with symptoms ranging from mild upper respiratory tract infections to severe respiratory failure and other serious complications due to viral replication. Therefore, identifying new prognostic factors is crucial in the management of influenza patients and complications associated with the disease. In this context, biomarkers such as NLR, PLR, and SIRI have been widely studied. Our study found that these indices were significantly elevated in patients diagnosed with influenza B compared to the control group, with positive correlations observed between NLR, PLR, and SIRI values and hospitalization requirements in influenza B patients.

The typical clinical presentation of influenza infection includes sudden-onset fever, headache, muscle pain, and fatigue. In our study, common symptoms in influenza B-positive patients were identified as cough, shortness of breath, fatigue, myalgia, fever, headache, and sore throat. A study by Wansaula and colleagues on severe acute respiratory infections reported similar findings regarding symptom frequency and order, aligning with our results. Similar symptom frequencies have also been reported in influenza-positive cases [13].

NLR is a widely used marker of systemic inflammation that can be quickly and cost-effectively measured through routine complete blood counts. Its use as a biomarker has increased in recent years. A study by Günay et al. examined the relationship between NLR and COPD exacerbations, finding NLR averages of 2.59 ± 1.79 in stable COPD patients and 4.28 ± 4.12 during exacerbations [14]. Another study emphasized NLR as a rapid, cost-effective predictor for early sepsis detection [15]. Liberski and colleagues investigated the diagnostic accuracy of NLR for sepsis in ICU admissions [16]. Additionally, NLR was found to be an early marker of poor prognosis in COVID-19 patients, with significantly higher levels in deceased patients compared to survivors [17,18]. A retrospective study on influenza B evaluated 122 patients and 119 controls, finding an NLR of 4.3 (2.92-6.49) in the patient group and 1.68 (1.22-2.07) in the control group, with a significantly elevated NLR in the patient group ($p<0.001$). This study reported an NLR cut-off of 2.51, with 86.9% sensitivity and 87.4% specificity [9]. In our study, we determined a median NLR of 6.11 (1.76-17.15). Limited mortality data prevented a comprehensive analysis, yet we found that hospitalized patients had an NLR of 8.61 (4.10-17.15) compared to 5.12 (1.76-6.68) in outpatients, a statistically significant difference. When we set the NLR threshold at 2.36, sensitivity was 96.7% and specificity 100% . A recent study comparing NLR in obstructive sleep apnea syndrome (OSAS) patients found significantly

higher average NLR in the OSAS group (1.76±0.77) compared to the control group (1.31±0.74) [19]. Similarly, we found significantly higher NLR in the patient group than in controls.

Although the role of platelets in inflammation pathogenesis is still debated, studies have shown that platelets contribute to cytokine production, playing an active role in the inflammatory process alongside their immunomodulatory functions. PLR, calculated as the ratio of platelet count to lymphocyte count in routine blood tests, has been investigated in patients with influenza B. One study found that PLR was significantly higher in the patient group compared to controls with a PLR cut-off of 147.99 [9]. In our study, the PLR threshold was set at 153.41 (AUC = 0.988, sensitivity: 93.3%, specificity: 92.9%), demonstrating high diagnostic accuracy. Similar studies have shown that PLR is significantly higher in patient groups than in healthy controls, supporting its diagnostic value [9,10].

During heightened inflammatory states, neutrophils increase as indicators of innate immune response, while lymphocytes, which provide primary immune defense against viruses, decline as disease severity increases. SIRI incorporates both neutrophil and lymphocyte counts, making it an effective marker for evaluating inflammation and immune response. Prior studies have explored SIRI's utility in predicting outcomes in other diseases, including stroke, pancreatitis, and cervical cancer [20-23]. SIRI also demonstrated the highest AUC in predicting peripheral artery disease in diabetic patients [24]. While there are no studies specifically on SIRI in influenza patients, our study shows that SIRI yielded a high AUC and that its levels were significantly elevated in both the patient group and hospitalized patients compared to the control group and outpatients.

Conclusions

Our study suggests that NLR, PLR, and SIRI are significant markers for identifying and managing influenza B in adult patients. These indices were found to be significantly elevated in patients with influenza B compared to the control group, and their levels were positively correlated with the need for hospitalization. Given the high sensitivity and specificity of these markers, they can provide valuable prognostic information for clinicians. However, due to the limited sample size and the lack of comparisons with other viral infections, further studies, including larger multi-center, prospective, randomized controlled trials, are required to validate these findings.

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Table 1. Demographic data of patients.

Mean Age (SD)	53.36 ± 14.05
Gender, n (%)	
Male	72 (55.3%)
Female,	58 (44.6%)
Comorbid Conditions, n (%)	
Cardiovascular disease	63 (48.5%)
Diabetes Mellitus	41 (31.5%)
Chronic Obstructive Pulmonar Disease (COPD)	33 (25.4%)
Asthma	30 (23.0%)
Neurological disease	11 (8.5%)
Presenting Symptoms, n (%)	
Cough	100 (76.9%)
Shortness of breath	90 (69.2%)
Fatigue	89 (68.5%)
Myalgia	73 (56.1%)
Fever	55 (42.3%)
Headache	46 (35.4%)
Sore throat	41 (31.5%)
Sputum	35 (26.9%)
Chest pain	21 (16.1%)
Nausea/Vomiting	19 (14.6%)
Runny nose	18 (13.8%)
Antiviral Treatment, n (%)	
Not given	17 (13.1%)
Given	113 (86.9%)
Antibiotic Treatment, n (%)	
Not given,	63 (48.5%)
Given	67 (51.5%)
Patient Monitoring, n (%)	
Hospitalized	57 (43.8%)
General ward	51 (39.2%)
Intensive care	6 (4.6%)
Outpatient	73 (56.1%)

Table 2. Comparison of laboratory findings between influenza B diagnosed patients and the control group.

	Influenza B Group mean±SD, Median [Min-Max]	**Control Group mean±SD, Median [Min-Max]**	**p**
Number of Cases, n	130	130	1.000
Gender, n (male, %)	72(55.3%)	81 (62.3%)	0.751
Age (Years)	53.36 ± 14.05	57.57 ± 15.68	0.378
WBC (10^9/L)	10.53 (5.41-19.83)	7.06 (4.6-10.9)	**0.001**
Neutrophil (10^9/L)	8.48 (4.1-16.3)	3.83 (2.4-6.3)	**0.001**
Lymphocyte (10^9/L)	1.46 (0.49-2.67)	2.54 (1.6-3.8)	**0.001**
PLT (10^9/L)	370 (188-548)	260 (173-336)	**0.001**
Monocyte (10^9/L)	0.58 (0.25-0.96)	0.5 (0.4-0.8)	0.357
NLR	6.11 (1.76-17.15)	1.63 (0.45-2.22)	**0.001**
PLR	266.66 (138.20-914.28)	99.21 (61.84-169.37)	**0.001**
SIRI	3.56 (0.82-10.11)	0.73 (0.45-1.48)	**0.001**

WBC, white blood cells; PLT, platelet count; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SIRI, systemic inflammation response index.

Table 3. ROC analysis results of neutrophil/lymphocyte ratio, PLR platelet/lymphocyte ratio and systemic inflammation response index values in differentiating influenza B and control groups.

	Cut-off Value	Sensitivity %	Specificity %	AUC (95%)	p
NLR	2.36	96.7	100	0.992 (0.972-1.000)	**0.001**
PLR	153.41	93.3	92.9	0.988 (0.962-1.000)	**0.001**
SIRI	1.36	93.1	92.9	0.977 (0.940-1.000)	**0.001**

NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SIRI, systemic inflammation response index.

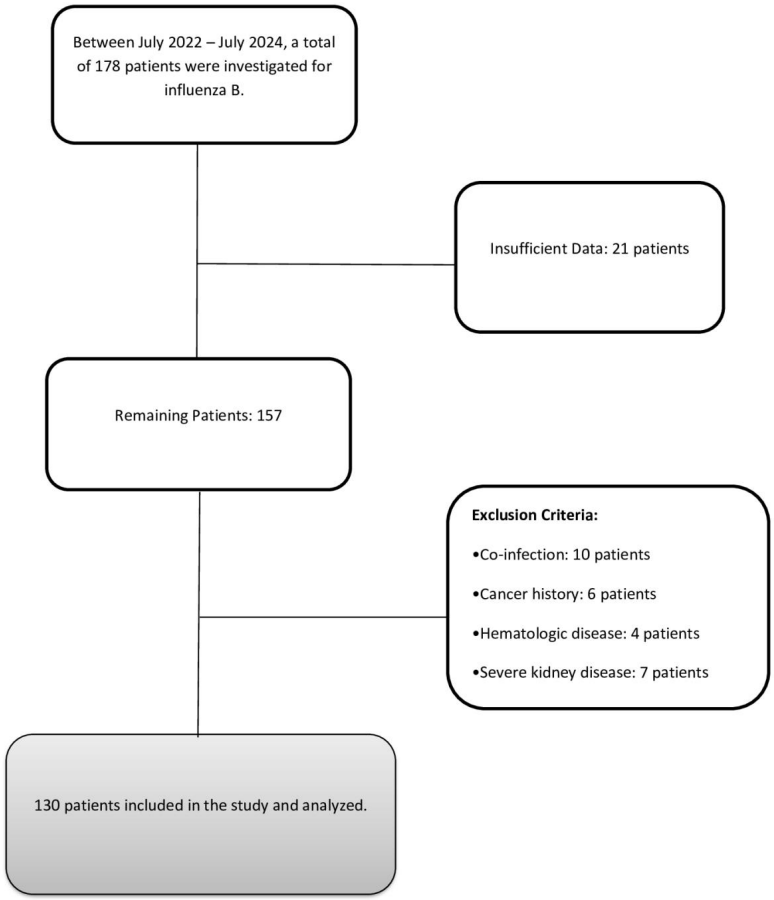

Figure 1. Flowchart.

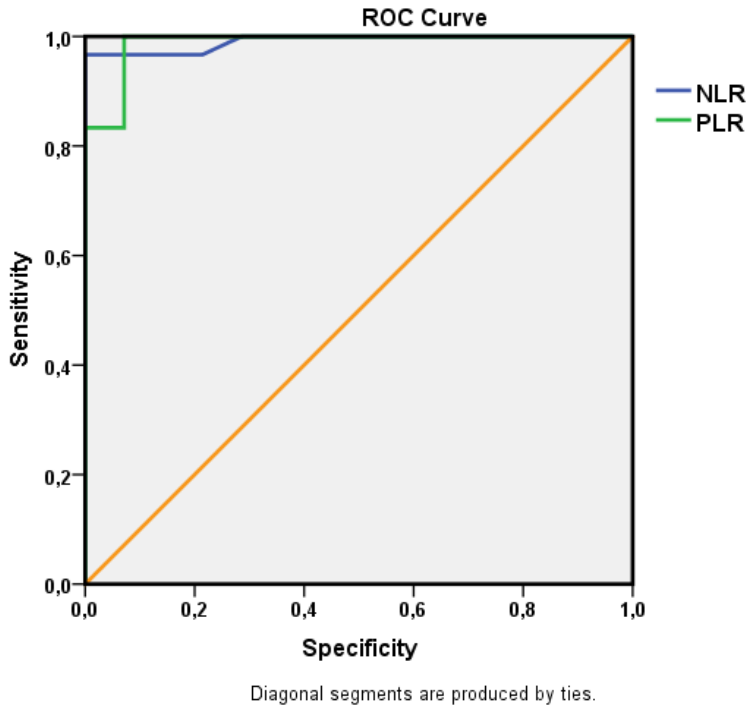

Figure 2. ROC Analysis of NLR and PLR Values for Influenza B Diagnosis. The figure presents the diagnostic performance and ROC curves of NLR and PLR compared to the control group.

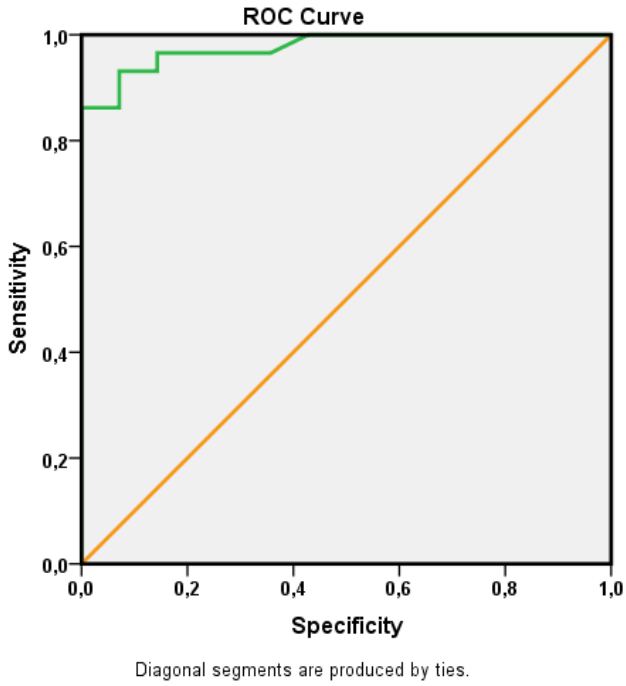

Figure 3. ROC Analysis of SIRI Value in Influenza B Diagnosis. The figure presents the diagnostic performance of SIRI and the ROC curve in comparison with the control group.