



Comparison of next-generation inflammatory indices in influenza A and B infections

Eurasian Clinical and Analytical Medicine Original Research

Inflammatory indices in influenza A and B

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Abstract

Objective: Influenza A and influenza B infections may differ in clinical course and inflammatory response. This study aimed to compare conventional hematological parameters and next-generation inflammatory indices in patients with influenza A and influenza B infections and to evaluate type-related differences in systemic inflammation.

Methods: This retrospective observational study included adults (≥ 18 years) presenting to the pulmonary clinic with flu-like symptoms and RT-PCR-confirmed influenza A or B infection. Demographic characteristics and laboratory parameters at presentation were recorded. Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammatory index (SII), systemic inflammatory response index (SIRI), and pan-immune inflammation value (PIV) were calculated. Discriminative performance was assessed using ROC analysis and multivariate logistic regression.

Results: A total of 363 patients were included, comprising 232 with influenza A and 131 with influenza B. Patients with influenza A were significantly older than those with influenza B. CRP, leukocyte and neutrophil counts, as well as NLR, SII, SIRI, PIV, and MLR values, were significantly higher in the influenza A group. Although individual biomarkers showed limited discriminative ability, multivariate logistic regression improved type classification, yielding an AUC of 0.727.

Conclusion: Influenza A infection is associated with a more pronounced systemic inflammatory response than influenza B. Next-generation inflammatory indices derived from routine laboratory tests may provide useful information for clinical evaluation. The combined assessment of multiple parameters may improve differentiation between influenza A and influenza B.

Keywords

Influenza A, Influenza B, inflammation, neutrophil-lymphocyte ratio, systemic inflammatory response index

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Introduction

Influenza is a major cause of acute viral respiratory tract infection worldwide and is associated with substantial morbidity and mortality.^{1,2} Clinical manifestations range from mild upper respiratory symptoms to severe pneumonia, acute respiratory failure, and multiple organ dysfunction, particularly in older adults, individuals with comorbidities, and immunocompromised patients.^{3,4}

Influenza A and influenza B differ in their epidemiological characteristics, clinical severity, and complication risk. Influenza A is generally associated with larger outbreaks, pandemics, and more severe disease, whereas influenza B is typically confined to seasonal epidemics with a relatively milder clinical course.^{5,6} However, differences in the inflammatory response between these types remain incompletely understood. Since the host inflammatory response is a major determinant of disease severity and prognosis, laboratory biomarkers have an important role in patient assessment.⁷ Conventional markers, including C-reactive protein (CRP), leukocyte count, and differential leukocyte ratios, are widely used in clinical practice.⁸ More recently, next-generation inflammatory indices derived from routine hematological parameters, such as the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune inflammation value (PIV), have emerged as promising indicators of systemic inflammation and prognosis in infectious and inflammatory diseases.^{9–14}

Despite their growing clinical use, evidence regarding the ability of these indices to distinguish between influenza A and influenza B remains limited. Therefore, this study aimed to compare conventional hematological parameters and next-generation inflammatory indices in patients with RT-PCR-confirmed influenza A and influenza B infections and to evaluate their potential role in identifying type-related differences in systemic inflammatory responses.

Materials and Methods

Study Design

This retrospective observational study was conducted in the pulmonary outpatient clinic of a tertiary care university hospital between January 2024 and January 2026. Adult patients (≥18 years) presenting with

influenza-like illness and having RT-PCR-confirmed influenza A or influenza B infection were consecutively included. The study aimed to compare inflammatory responses and next-generation inflammatory indices between patients with influenza A and influenza B infections. Influenza-like illness was defined as the acute onset of fever accompanied by respiratory or systemic symptoms, including cough, sore throat, rhinorrhea, nasal congestion, chills, malaise, myalgia, arthralgia, or headache. Patients with concomitant bacterial infection (defined as positive microbiological culture results or elevated procalcitonin levels), those receiving immunosuppressive therapy, patients with hematological malignancies, and those with incomplete laboratory data were excluded.

Data Collection and Laboratory Measurements

Demographic characteristics (age and sex) and laboratory data obtained at the time of outpatient admission were retrospectively collected from the hospital's electronic medical records.

Influenza A and influenza B infections were confirmed using the Bio-Speedy® Respiratory Tract Multiplex RT-qPCR Kit (Bioeksan Inc., Ankara, Türkiye) according to the manufacturer's instructions.

Laboratory parameters included leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts, hemoglobin concentration, and red cell distribution width (RDW).

The following inflammatory indices were calculated:

- Neutrophil-to-lymphocyte ratio (NLR) = neutrophil count / lymphocyte count
- Monocyte-to-lymphocyte ratio (MLR) = monocyte count / lymphocyte count
- Platelet-to-lymphocyte ratio (PLR) = platelet count / lymphocyte count
- Systemic Immune-Inflammation Index (SII) = neutrophil × platelet / lymphocyte
- Systemic Inflammation Response Index (SIRI) = neutrophil × monocyte / lymphocyte
- Pan-Immune Inflammation Value (PIV) = neutrophil × platelet × monocyte / lymphocyte
- Hemoglobin-to-RDW ratio (Hb/RDW) = hemoglobin / RDW

Ethical Approval

The study protocol was approved by the Başkent University Institutional Review Board (Date: 04.02.2026, No: KA26/64).

Table 1. Comparison of demographic and laboratory parameters in patients with influenza A and B.

Variable	A Median (IQR)	B Median (IQR)	P	P_FDR	Effect size
Age (years)	44 [33.8–58.0]	37 [28.5–43.5]	4.06E–09	6.91E–08*	.372
Leukocyte	6.54 [5.13–8.21]	5.79 [4.44–7.45]	.0043	.0091*	.180
Neutrophil	4.55 [3.35–6.03]	3.90 [2.80–5.04]	.0010	.0023*	.209
Lymphocyte	1.11 [0.83–1.65]	1.22 [0.90–1.69]	0.1560	0.2040	-0.090
Monocyte	0.603 [0.434–0.747]	0.553 [0.410–0.746]	0.2152	0.2613	.078
Platelet	202 [169–242]	189 [160–230]	.0738	0.1046	.113
Hemoglobin	13.8 [12.8–15.1]	14.2 [13.2–15.3]	.0425	.0657	-0.211
RDW	11.9 [11.1–13.0]	12.0 [11.6–12.8]	0.4550	0.5157	-.047
CRP	211 [9.78–38.6]	101 [4.65–22.0]	2.37E–07	2.02E–06*	.326
NLR	4.23 [2.57–6.16]	2.94 [2.04–4.74]	.0006	.0017*	.217
SII	777 [498–1280]	552 [416–913]	.0002	.0013*	.233
SIRI	2.42 [1.28–3.87]	1.62 [1.07–2.60]	.0004	.0014*	.224
PIV	459 [256–748]	318 [188–548]	.0004	.0014*	.223
MLR	0.515 [0.364–0.713]	0.451 [0.325–0.613]	.0153	.0288*	.153
PLR	171 [122–242]	155 [110–209]	.0417	.0657	.129
Hb/RDW	1.18 [1.01–1.33]	1.18 [1.04–1.32]	.5047	.5363	-0.042

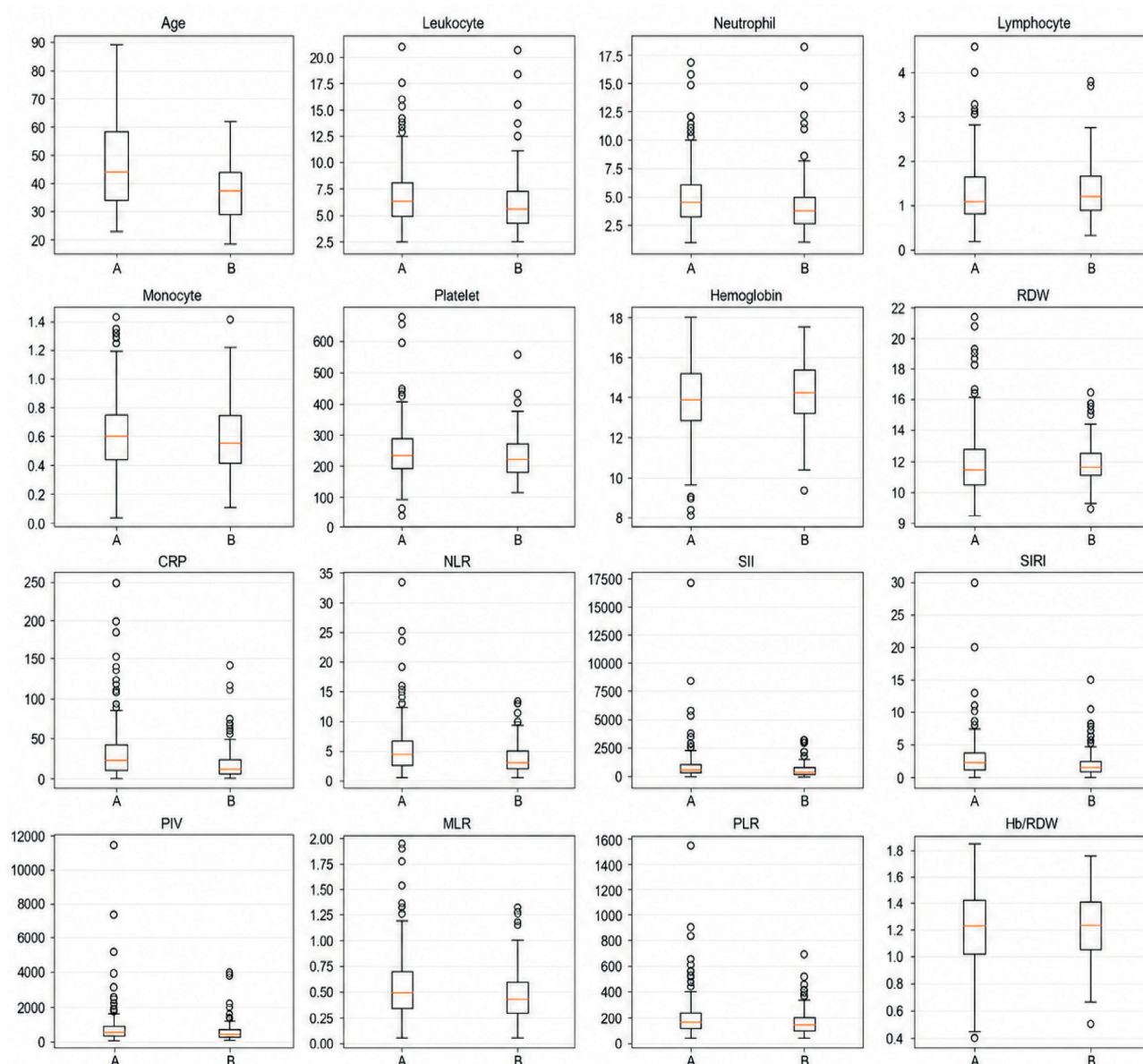


Figure 1. Comparison of the distributions of demographic and laboratory parameters in patients with influenza A and B (box plots)

Statistical Analysis

All statistical analyses were performed using Python in the Google Colab environment with the pandas, NumPy, SciPy, and statsmodels libraries. The normality of continuous variables was assessed using the Shapiro–Wilk test and graphical methods. Normally distributed variables were compared using Welch’s t-test, whereas non-normally distributed variables were analyzed using the Mann–Whitney U test. Categorical variables were compared using the chi-square test. Continuous variables are presented as mean $\pm$ standard deviation or median [interquartile range (IQR)], as appropriate, and categorical variables as frequency and percentage.

To account for multiple comparisons, the Benjamini–Hochberg false discovery rate (FDR) correction was applied, with adjusted *P* values $< .05$ considered statistically significant. Effect sizes were calculated using Cohen’s *d* for parametric analyses and Cliff’s delta for nonparametric analyses.

Spearman correlation analysis was performed separately for the influenza A and influenza B groups. Receiver operating characteristic (ROC) analysis was used to evaluate the discriminatory performance of individual variables, and the area under the ROC curve (AUC) was calculated. A multivariate logistic regression model was constructed

to identify independent predictors of influenza type. Continuous variables were standardized before model development, and results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Model performance was evaluated using the AUC.

Reporting Guidelines

This study was reported in accordance with the STROBE guideline.

Results

Patient Characteristics

A total of 363 patients were included, comprising 232 (63.9%) patients with influenza A and 131 (36.1%) with influenza B. There were no significant differences in sex distribution between the groups ($P > .05$). Detailed demographic characteristics and laboratory findings are presented in Table 1.

Patients with influenza A were significantly older than those with influenza B (median age: 44 vs. 37 years, $p\text{FDR} < .001$). In addition, CRP, leukocyte count, neutrophil count, NLR, MLR, SII, SIRI, and PIV were significantly higher in the influenza A group (all $p\text{FDR} < .05$), with effect sizes ranging from small to moderate (Figure 1). No significant differences were observed in lymphocyte count, monocyte count, platelet count, RDW, PLR, or Hb/RDW ratio after FDR correction (Table 1).

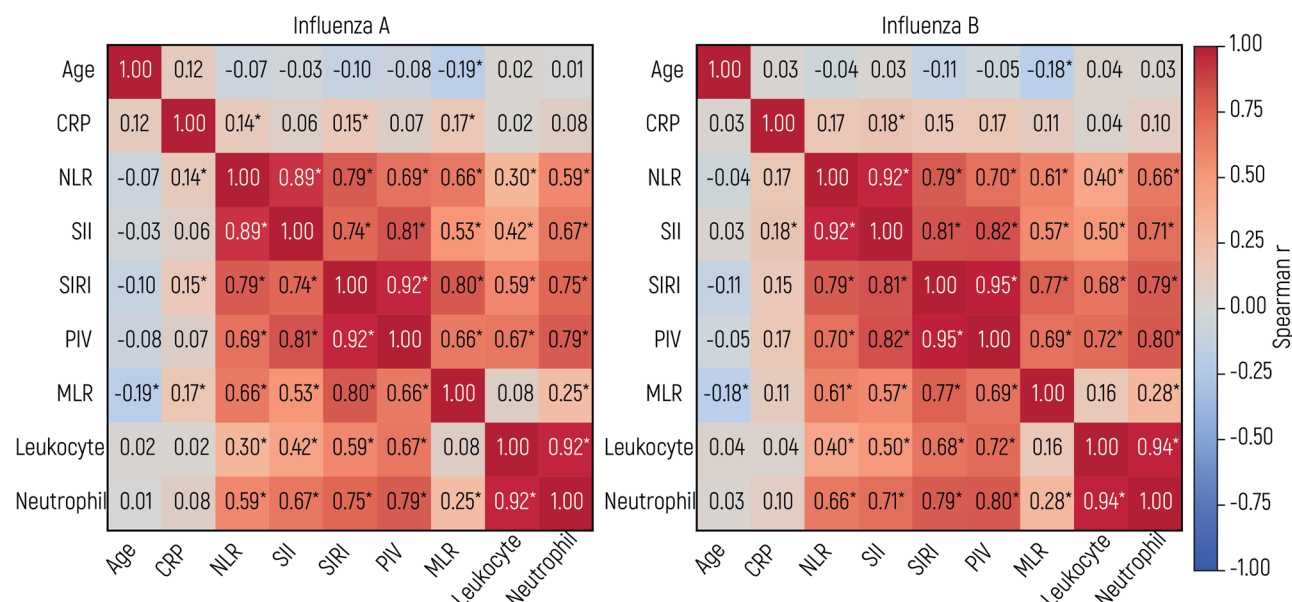


Figure 2. Spearman correlation matrix between demographic, hematological, and inflammatory parameters in patients with Influenza A (left) and Influenza B (right).

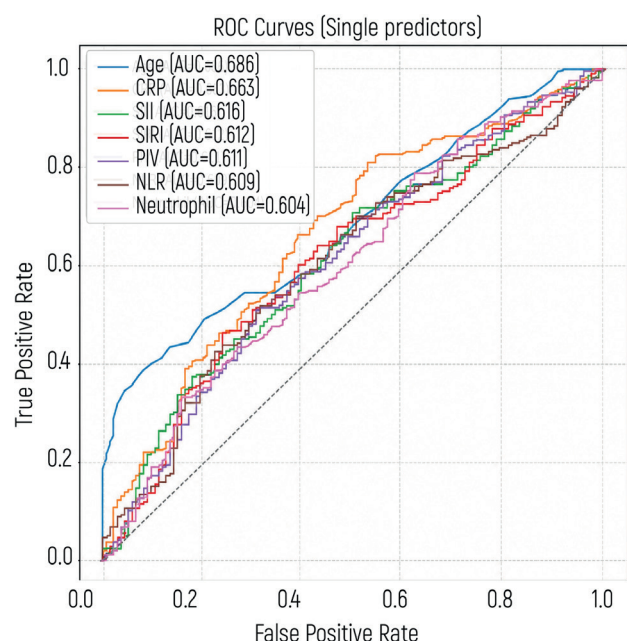


Figure 3. ROC curves of the individual variables with the highest discriminatory power in differentiating between influenza A and influenza B.

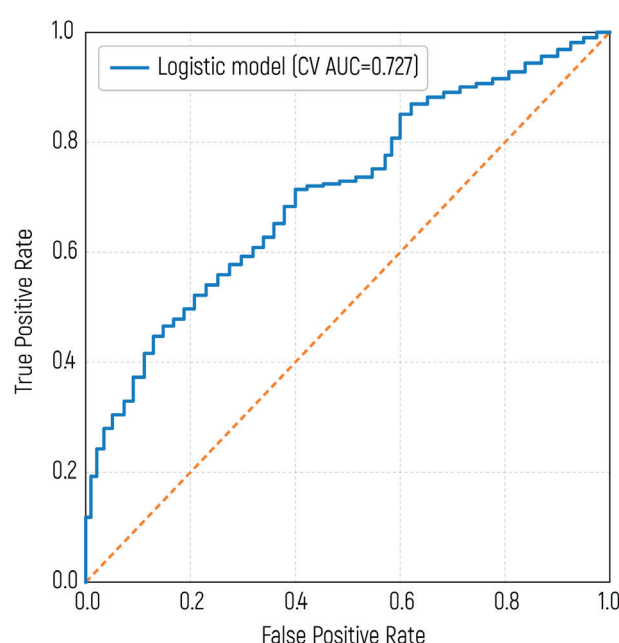


Figure 4. ROC curve of the multivariate logistic regression model for differentiating between influenza A and influenza B.

Correlation Analysis

Spearman correlation analysis demonstrated strong positive correlations among NLR, SII, SIRI, and PIV in both influenza A and influenza B groups (Figure 2). Leukocyte and neutrophil counts were moderately to strongly correlated with these inflammatory indices. Age showed only weak correlations with laboratory parameters; however, a weak negative correlation between age and MLR was observed in the influenza A group.

ROC Analysis

ROC analysis demonstrated limited-to-moderate discriminatory performance for individual biomarkers (Figure 3). Age showed the highest AUC (0.686), followed by CRP (0.663), SII (0.616), SIRI (0.612), PIV (0.611), NLR (0.609), neutrophil count (0.604), leukocyte count (0.590), and MLR (0.577). Overall, individual biomarkers alone showed limited ability to distinguish influenza A from influenza B.

Multivariate Logistic Regression

In multivariate logistic regression analysis, age (OR = 2.54, $P < .001$), CRP (OR = 1.78, $P = .001$), and leukocyte count (OR = 5.10, $P = .031$) were independently associated with influenza A, whereas PIV (OR = 0.10, $P = .038$) and neutrophil count (OR = 0.17, $P = .039$) showed inverse associations. NLR, SII, SIRI, and MLR were not independent predictors (Table 2). The multivariate model demonstrated improved discriminatory performance compared with individual biomarkers, achieving an AUC of 0.727 (Figure 4).

Discussion

Hematological parameters have been widely investigated for the diagnosis and differential diagnosis of influenza infections. Previous studies have shown that neutrophil and lymphocyte counts, particularly the neutrophil-to-lymphocyte ratio (NLR), reflect the inflammatory

Table 1. ROC curves of the individual variables with the highest discriminatory power in differentiating between influenza A and influenza B.

Variable	Odds Ratio (OR)	95% Confidence Interval	P value
Age	2.54	1.85 – 3.50	<0.001*
CRP	1.78	1.25 – 2.54	0.001*
PIV	0.10	0.01 – 0.88	0.038*
Leukocyte	5.10	1.16 – 22.51	0.031*
Neutrophil	0.17	0.03 – 0.91	0.039*
NLR	1.11	0.28 – 4.44	0.887
SII	5.36	0.58 – 49.86	0.140
SIRI	4.31	0.55 – 34.07	0.166
MLR	1.02	0.53 – 1.96	0.962

response more effectively than individual hematological parameters. Combined indices, such as NLR and platelet-to-neutrophil ratio (PNR), have also been reported to improve the differentiation of influenza from bacterial infections, highlighting the increasing clinical value of ratio-based inflammatory markers in viral diseases.¹⁵ In the present study, leukocyte count, neutrophil count, NLR, SII, SIRI, PIV, and CRP were significantly higher in patients with influenza A than in those with influenza B. However, ROC analysis demonstrated only limited-to-moderate discriminatory performance of these individual biomarkers, suggesting that although inflammatory indices are useful for identifying systemic inflammation, they have limited ability to distinguish between influenza types.

Our findings are consistent with previous studies reporting that NLR and PLR alone are insufficient for differentiating influenza pathogens, whereas combinations of inflammatory markers provide superior diagnostic performance.¹⁶ Similarly, PLR and Hb/RDW did not differ significantly between influenza A and B, indicating that platelet-based indices may reflect systemic inflammation but appear less sensitive to differences between influenza A and influenza B.

Although CRP and leukocyte count showed only moderate discriminatory performance individually, the multivariate logistic regression model showed greater apparent discriminatory performance than individual variables (AUC = 0.727). Likewise, previous studies have shown that combining routine inflammatory markers improves diagnostic performance compared with individual biomarkers.^{16,17} These findings support the concept that influenza-related inflammatory responses are multidimensional and are more accurately evaluated using multiple variables rather than a single laboratory parameter.

The limited diagnostic performance observed in our study is also consistent with findings from other infectious diseases. Previous studies have demonstrated that inflammatory indices such as NLR, SII, SIRI, and PIV generally show poor-to-moderate predictive performance when used individually and should be interpreted together with clinical findings.¹⁸ Likewise, multivariable prediction models, including logistic regression and machine-learning algorithms, consistently achieve higher discriminatory performance than single biomarkers.^{17,19,20} Although the CatBoost model reported by previous investigators achieved higher AUC values than our logistic regression model, the latter offers the advantage of being simple, transparent, and easily applicable in routine clinical practice.¹⁹

CRP represents another important finding of this study. Previous investigations comparing respiratory viral infections reported significantly higher CRP levels in SARS-CoV-2 infection than in influenza and other respiratory viruses.²¹ In the present study, CRP levels were also significantly higher in influenza A than in influenza B, suggesting that the magnitude of systemic inflammation differs even between

influenza types. Nevertheless, both our findings and previous reports indicate that CRP should be regarded as a supportive rather than definitive diagnostic biomarker.^{17,18,21}

Strong positive correlations among NLR, SII, SIRI, and PIV observed in this study indicate that these indices largely represent overlapping aspects of the same inflammatory process. Similar correlations have been reported in other inflammatory diseases.^{18,22} Their loss of significance in the multivariate model is therefore likely explained by collinearity, suggesting that measuring multiple highly correlated indices simultaneously may provide limited additional clinical value.

The present study has several strengths. To our knowledge, it is among the few studies evaluating multiple next-generation inflammatory indices, including SII, SIRI, and PIV, simultaneously in adult patients with influenza A and influenza B. Furthermore, integrating these indices with demographic and laboratory variables in a multivariate model demonstrated greater apparent discrimination between influenza A and influenza B than individual biomarkers.

Limitations

This study has several limitations. First, its retrospective design precludes the establishment of causal relationships and may have introduced variability in the timing and completeness of clinical data collection. Second, the single-center setting may limit the generalizability of the findings. Third, influenza A subtyping (e.g., H1N1 or H3N2) and influenza B lineage determination (Victoria or Yamagata) were not routinely performed; therefore, subtype- and lineage-specific hematological differences could not be evaluated. Finally, inflammatory markers were assessed only at hospital presentation, and the absence of serial measurements prevented evaluation of temporal changes in inflammatory indices and their association with disease progression.

Conclusion

In conclusion, adult patients with influenza A exhibited a more pronounced systemic inflammatory response than those with influenza B, as reflected by higher CRP levels, leukocyte and neutrophil counts, and next-generation inflammatory indices, including NLR, SII, SIRI, PIV, and MLR. Although the discriminatory performance of individual biomarkers was limited, combining demographic and laboratory variables in a multivariate logistic regression model showed greater apparent discrimination between influenza A and influenza B (AUC = 0.727). These readily available inflammatory indices may help characterize differences in systemic inflammatory responses between influenza A and influenza B but should complement rather than replace molecular diagnostic methods. Prospective multicenter studies are needed to further validate their clinical and prognostic utility.

Declarations

Animal and Human Rights Statement

All procedures involving human participants were performed in accordance with the ethical standards of the institutional ethics committee and the Declaration of Helsinki.

Informed Consent

The requirement for informed consent was waived by the Institutional Review Board due to the study's retrospective design.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

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None.

Author Contributions (CRediT Taxonomy)

Conceptualization: YU, GU, KUK

Methodology: YU

Data curation: YU, MK

Formal analysis: YU, GU

Investigation: YU, MK, KUK

Writing – original draft: YU, MK, KUK

Writing – review & editing: YU, GU

Supervision: GU, KUK

AI Usage Disclosure

The authors used artificial intelligence (AI)-assisted tools solely to improve the language, grammar, and readability of the manuscript. All scientific content, data interpretation, and conclusions were developed, verified, and approved by the authors, who take full responsibility for the final manuscript.

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