

Influenza A (H1N1) and COVID-19 Pneumonias: An Evaluation in the Light of New Hematologic Indices

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Objective: Influenza A (H1N1) and COVID-19 viruses are two very different airway viral pneumonia agents that cause similar clinical manifestations and coinfections. The aim of this study was to investigate new laboratory indices, clinical and radiological findings that may help in the differential diagnosis of these two viral pneumonias.

Material and Methods: Eighty-nine hospitalized patients, 38 with Influenza A (H1N1) and 51 with COVID-19 pneumonia, were retrospectively analyzed. Laboratory parameters, clinical, and radiological findings of the patients were obtained from their medical files. Numerous hematological and biochemical parameters (neutrophil, monocytes, mean corpuscular volume (MCV), albumin, uric acid, etc) were investigated and new indices (neutrophil/albumin ratio (NAR), lymphocyte-monocyte ratio (LMR), etc) were calculated. Both viral pneumonias were compared in terms of new hematological and biochemical indices and clinical and radiological outcomes.

Results: In terms of clinical symptoms, fever, cough, and shortness of breath were higher in influenza A (H1N1) pneumonia, while sore throat, headache, and malaise were higher in COVID-19 pneumonia. Consolidations in influenza A (H1N1) pneumonia and round ground-glass opacities in COVID-19 pneumonia were found as typical radiologic findings. The laboratory parameters most associated with COVID-19 pneumonia were monocytes (OR 27.327, %95 CI: 4.143–180.234, $p=0.001$), MCV (OR 1.130, %95 CI: 1.011–1.262, $p=0.031$), albumin (OR 0.314, %95 CI: 0.111–0.888, $p=0.029$) and uric acid (OR 1.631, %95 CI: 1.055–2.522, $p=0.028$), and laboratory indices were LMR (OR 0.677, %95 CI: 0.492–0.933, $p=0.017$) and NAR (OR 1.514, %95 CI: 1.004–2.282, $p=0.048$).

Conclusion: The most significant laboratory parameters predictive of COVID-19 pneumonia were monocytes, uric acid, albumin, and MCV and the most effective indices were LMR and NAR. Round ground glass opacities were the primary radiological findings suggestive of COVID-19 pneumonia.

Keywords: influenza A (H1N1), COVID-19 pneumonia, hematologic indices, lymphocyte-monocyte ratio, neutrophil-albumin ratio

Introduction

The coronavirus pandemic, caused by the SARS-CoV-2 outbreak in 2019, is still a public health concern worldwide.¹ Influenza A (H1N1), on the other hand, occurs mostly in winter and affects 5–10% of adults each year.² These two viruses show significant similarities in terms of symptoms, clinical presentation and transmission route.³ COVID-19 is associated with adverse outcomes such as coagulation disorders, respiratory distress syndrome, organ failure, serious illness, and systemic inflammation.^{4,5} Therefore, early detection of critically ill COVID-19 patients and differential diagnosis from other viral infections are important goals. The diagnosis of Influenza A (H1N1) and COVID-19 infection is mainly based on proving the confirmation of the presence of the virus by reverse transcription polymerase chain reaction (RT-PCR) analysis, but its applicability to every patient is limited as it is time-consuming, expensive, and requires specialized equipment.⁶ Many studies have investigated the importance of data such as gender, age, biochemical and hematologic parameters, and computed tomography (CT) findings in making the diagnosis and determining prognosis.⁷

Inflammation is a well-known symptom of numerous infectious diseases. The evidence indicates that inflammatory reactions are crucial in the management of COVID-19 and especially in the development of many viral pneumonias.⁸ Complete blood count (CBC) parameters have been investigated in many diseases as indicators of the inflammatory process.⁹ Peripheral white blood cell (WBC) counts, including differential subsets of neutrophils, lymphocytes, eosinophils, monocytes, and basophils, are recognized as useful biomarkers for a systemic inflammation and immune response. Platelets also have an important role in coagulation, in innate immunity, and in inflammatory reactions.^{10,11} Parameters such as ferritin, lymphocyte and platelet counts, D-dimer, and lactate dehydrogenase (LDH), which can be easily studied in routine laboratories, are frequently used to predict disease severity and mortality.¹² Due to the variability and limited specificity of blood parameters in patients, efforts are ongoing to obtain cheaper, more accessible, and more specific parameters.¹³

Many new hematologic indices that provide insight into the cellular immune and systemic inflammatory responses, are easily obtainable, inexpensive, and important in indicating disease severity and mortality have been emphasized.¹⁴ Indeed, CBC parameters used alone or in ratio to each other (such as neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), lymphocyte–monocyte ratio (LMR), systemic immune inflammation index (SII), aggregate index of systemic inflammation (AISI), systemic inflammatory response index (SIRI)) can be useful as indices of both inflammation and immunity in many diseases and tumors, especially lung and colorectal cancer. NLR and PLR have been reported to be beneficial prognostic factors for COVID-19 severity.^{15–17}

Many laboratory indices have been studied as inexpensive, easily measurable and reproducible tests for the differential diagnosis, disease severity and mortality of COVID-19 and influenza A (H1N1) pneumonia. However, many studies in this field have focused on a few of these indices separately.

In our study, laboratory parameters (WBC, red blood cell distribution width (RDW), mean corpuscular volume (MCV), mean platelet volume (MPV), platelets (PLT), C-reactive protein (CRP), LDH, blood urea nitrogen (BUN), triglyceride (TG), procalcitonin, creatinine, albumin, bilirubin, uric acid), and indices (NLR, PLR, LMR, lymphocyte–CRP ratio (LCR), CRP–lymphocyte ratio (CLR), neutrophil–monocyte ratio (NMR), RDW–albumin ratio (RAR), CRP–albumin ratio (CAR), BUN–albumin ratio (BAR), neutrophil–albumin ratio (NAR), the C-reactive protein–albumin–lymphocyte (CALLY) index, albumin–bilirubin (ALBI) score, hemoglobin, albumin, lymphocyte, and platelet (HALP) score, AISI, SII, SIRI) were analysed within a broad framework.

Accurate interpretation and use of biomarkers can help to understand the severity and character of inflammation and thus provide insight into the severity of disease and differential diagnosis from other pathogens. In light of all these studies, we aimed to find the most effective index in the differential diagnosis of two viral diseases by considering whole blood parameters and indices derived from them in a very broad framework.

Materials and Methods

Study Design and Population

Our study was planned as a retrospective and observational cohort analysis. Clinical, radiological, and laboratory data of 51 cases with confirmed COVID-19 etiology between October and December 2020 and 38 cases with confirmed influenza A (H1N1) virus etiology between January and May 2018 were retrospectively analyzed. COVID-19 diagnosis was confirmed according to World Health Organization recommendations.¹⁸ In this study, only patients older than 18 years with a positive RT-PCR test on nasal-pharyngeal swabs were evaluated. Exclusion criteria included cases with negative RT-PCR tests, patients with hematological malignancies, and patients with missing RT-PCR and laboratory test results. All patients were primarily classified into two groups: Influenza A (H1N1) and COVID-19. These groups were compared in terms of clinical, laboratory, and radiologic findings. Secondly, each group was stratified into survivors and non-survivors, and laboratory parameters for in-hospital mortality were compared. This research was analyzed and approved by the Ethics Committee of Karamanoğlu Mehmetbey University on 05.02.2025, with the number 16–2025/11, and the criteria of the Declaration of Helsinki were taken into consideration throughout the study.

Demographic and Clinical Characteristics

Demographic characteristics (age and gender), clinical symptoms (such as fever, cough, and dyspnea) and comorbid conditions (such as COPD, CVD, and DM) of the patients were obtained from medical records, and the two groups were compared in terms of these characteristics.

Laboratory Analyses

The analyses included CBC (such as WBC, neutrophils, lymphocytes, monocytes, MCV, and PLT) and biochemical blood values (CRP, LDH, BUN, TG, albumin, and Uric acid). For the analysis, laboratory values measured on the day of admission to the hospital were considered. Routine hematologic and biochemical tests were performed as follows using normal reference values determined by the hospital's laboratory department: WBC ($4\text{--}10 \times 10^3/\mu\text{L}$), neutrophils ($2\text{--}7 \times 10^3/\mu\text{L}$); lymphocytes ($0.8\text{--}4 \times 10^3/\mu\text{L}$); monocytes ($0.12\text{--}1.20 \times 10^3/\mu\text{L}$); MCV (80–100 fL); RDW (35–56 fL); PLT ($100\text{--}380 \times 10^3/\mu\text{L}$); MPV (6.5–12 fL); CRP (0–5 mg/L); procalcitonin (0–0.5 $\mu\text{g/L}$); BUN (10–20 mg/dL); creatinine (0.84–1.25 mg/dL); TG (0–150 mg/dL); albumin (32–52 g/L); uric acid (3.5–7.2 mg/dL); total bilirubin (0.3–1.2 mg/dL). Serum biochemical tests were evaluated with the Advia-Centaur XP device (Siemens AG, Munich, Germany) auto analyzer and routine kits specific for each test. Hemogram parameters were measured using a Mindray BC 6800 (Mindray, Shenzhen, People's Republic of China) automated hematology analyzer. COVID-19 and Influenza A H1N1 were detected from nasopharyngeal swab samples using the RT-PCR assay. SARS-CoV-2 detection was performed on a Bio-Rad CFX96 real-time PCR platform (Bio-Rad Laboratories, California, USA) using the DirectDetect SARS-CoV-2 qPCR Kit (Coyote Bioscience Co., Ltd).

Calculated Indices

The indices obtained from blood analysis were calculated using the following equations: PLR (platelet to lymphocyte ratio); NLR (neutrophil to lymphocyte ratio); LCR (lymphocyte to CRP ratio), MLR (monocyte to lymphocyte ratio), CLR (CRP to lymphocyte ratio), LMR (lymphocyte to monocyte ratio), NMR (neutrophil to monocyte ratio), RAR (RDW to albumin ratio), BAR (BUN to albumin ratio), CAR (CRP to albumin ratio), NAR (neutrophil to albumin ratio), CALLY Index (serum albumin level (g/dl) $\times$ lymphocyte count (cells/ μ) / C-reactive protein (mg/dl) $\times$ 104); ALBI ($\log_{10}$ bilirubin (micro mol / L) $\times$ 0.66) + (albumin (g/L) $\times$ -0.085); HALP (hemoglobin (g/L) $\times$ albumin (g/L) $\times$ lymphocyte (109/L)) / platelet (109/L); AISI (neutrophil (109/L) $\times$ platelet (109/L) $\times$ monocyte (109/L)) / lymphocyte (109/L); SII (platelets (109/L) $\times$ neutrophils (109/L)) / lymphocyte (109/L); SIRI (neutrophils (109/L) $\times$ monocyte (109/L)) / lymphocyte (109/L)).¹⁹

Radiological Assessment

Thoracic computed tomography (CT) examinations were performed using a multislice CT scanner (Alexion 16, TMS Corporation, Otawara, Japan) with a slice thickness of 1–2 mm. All images were acquired during a single breath hold in full inspiration, and standard reconstruction algorithms were applied. Thoracic CT findings of the patients were obtained from our hospital's radiology reports. Radiological findings were categorized as follows: appearance type (round/nodular ground-glass opacity (GGO), non-round diffuse/patchy GGO, patchy consolidation and GGO, lobar/segmentary consolidation, micronodular/interstitial densities), Involvement distribution (unilateral, bilateral), and pleural effusion (present/absent) (Table 1).

Statistical Analysis

In this study, the BM SPSS 22.0 statistical package program (IBM, Corp. Armonk, NY, USA) was employed to collect data. The conformity of the numerical data to normal distribution was analyzed by Shapiro–Wilk *W*-test and Kolmogorov–Smirnov test. Since the data were not normally distributed, descriptive data were given as median and 25th and 75th percentile values. Categorical variables were presented as numbers (n) and percentages (%). In independent groups, categorical variables were analyzed with the chi-square test, while continuous variables that did not fit the normal distribution were analyzed with the Mann–Whitney *U*-test. A *P* value below 0.05 was considered statistically meaningful. Univariate and multivariate logistic regression analyses were performed to evaluate the relationship and predictive power of the parameters with COVID-19 pneumonia. Odds ratio (OR) values and 95% confidence intervals (CI) determined as a result of the analyses are presented.

Table 1 Comparison of Demographic, Clinical, and Radiologic Characteristics Between COVID-19 and Influenza A (H1N1)

Characteristics	COVID-19 (n: 51)	Influenza A (H1N1) (n: 38)	p value
Age[#]	61.2 ± 16.4	59.3 ± 15.7	0.590 ^a
Gender (male/female)	20 (39.2%) / 31 (60.8%)	25 (65.8%) / 13 (34.2%)	0.013 ^b
Asthma	15 (29.4%)	2 (5.3%)	0.004 ^b
COPD	15 (29.4%)	20 (52.6%)	0.027 ^b
CVD	18 (35.3%)	7 (18.4%)	0.080 ^b
DM	6 (11.8%)	6 (15.8%)	0.582 ^b
Fever	15 (29.4%)	34 (89.5%)	<0.001 ^b
Cough	33 (64.7%)	37 (97.4%)	<0.001 ^b
Dyspnea	33 (64.7%)	37 (97.4%)	<0.001 ^b
Nausea-Vomiting	12 (23.5%)	12 (31.6%)	0.397 ^b
Joint pain	24 (47.1%)	15 (39.5%)	0.476 ^b
Sore throat	31 (60.8%)	14 (36.8%)	0.025 ^b
Headache	24 (47.1%)	8 (21.1%)	0.011 ^b
Fatigue	35 (68.6%)	7 (18.4%)	<0.001 ^b
CT image characteristics			
Appearance pattern			
Round/nodular GGO	28 (54.9%)	7 (18.4%)	<0.001 ^b
Non-rounded diffuse/patchy GGO	18 (35.3%)	5 (13.2%)	
Patchy consolidation and GGO	5 (9.8%)	12 (31.6%)	
Lobar/segmentary consolidation	0 (0.0%)	12 (31.6%)	
Micronodular/ interstitial densities	0 (0.0%)	2 (5.3%)	
Distribution of involvement			
Unilateral	9 (17.6%)	9 (23.7%)	0.483 ^b
Bilateral	42 (82.4%)	29 (76.3%)	
Pleural effusion	0 (0.00%)	5 (13.2%)	0.008
Intensive care unit	11 (20.6%)	10 (26.3%)	0.397 ^b
Clinical outcome (nonsurvivor/survivor)	3 (5.9%) / 48 (94.1%)	5 (13.15%) / 33 (86.8%)	0.235 ^b

Notes: [#]Results are presented as mean value and SD (standard deviation) and remaining results as n (%). ^aStudent's t-test, ^bChi-square test, p-value < 0.05 was considered statistically significant.

Abbreviations: COPD, Chronic obstructive pulmonary disease; CVD, Cardiovascular disease; DM, Diabetes mellitus; GGO, ground-glass opacity.

Results

The average age of 51 cases in the COVID-19 group was 61.2 ± 16.4 years, while the age of 38 cases in the Influenza A group was 59.3 ± 15.7 years. Age was not statistically significant in either pneumonia group (p=0.590) (Table 1). Gender difference was observed in these two pneumonia groups. COVID-19 pneumonia was higher in women, while influenza A (H1N1) pneumonia was higher in men (p=0.013) (Table 1). In terms of comorbidities, asthma was statistically increased in COVID-19 pneumonia and COPD in influenza A (H1N1) pneumonia, while CVD and DM did not differ between groups. Fever, cough, and dyspnea were significantly higher in influenza A (H1N1) pneumonia, while sore throat, headache, and fatigue were significantly higher in COVID-19 pneumonia (Table 1).

When CT image features were analyzed, round/nodular ground-glass opacity and non-round diffuse/patchy ground-glass opacity were significantly increased in COVID-19 pneumonia compared to influenza A (H1N1) pneumonia, while patchy consolidation and GGO, lobar/segmentary consolidation and micronodular/interstitial densities were the prominent radiologic appearance patterns in influenza A (H1N1) pneumonia (p<0.001). Bilateral and unilateral involvement did not differ significantly in both pneumonia groups (p=0.483), whereas pleural effusion was significantly higher in Influenza A (H1N1) pneumonia (p=0.008). The duration of intensive care unit (ICU) stay (p=0.397) and clinical outcome (ex/recovery) (p=0.235) did not significantly differ in both pneumonia groups (Table 1). Laboratory parameters including

WBC, neutrophil, monocyte, RDW, MCV, BUN, TG, procalcitonin, albumin, uric acid, as well as indices derived from Laboratory parameters such as NLR, MLR, LMR, RAR, BAR, NAR, AISI, SII, SIRI, showed a significant difference between COVID-19 pneumonia and influenza A (H1N1) pneumonia ($p<0.05$) (Table 2).

Ex and survivors in both COVID-19 and influenza A (H1N1) pneumonia groups were compared in terms of hematological parameters and indices indicating in-hospital mortality derived from them (Table 3). In the COVID-19 pneumonia group, WBC, lymphocyte, BUN, NLR, PLR, CLR, CAR, BAR, SII, SIRI, CALLY, HALP were identified significantly different in the ex and survivor groups ($p<0.05$). In the influenza A (H1N1) pneumonia group, LDH, BUN, TG, creatinine, albumin, RAR, CAR, BAR, NAR, AISI, SII, SIRI, CALLY, ALBI, HALP were found statistically different in the ex and survivor groups ($p<0.05$) (Table 3).

Two logistic regression models were created for diagnostic differentiation between COVID-19 and influenza A (H1N1) pneumonia. Univariate and multivariate logistic regression analyses were applied for laboratory parameters

Table 2 Comparison of Laboratory Characteristics Between COVID-19 and Influenza A (H1N1) Groups

Characteristics	COVID-19 (n: 51) Median (Q1-Q3)	Influenza A(H1N1)(n: 38) Median (Q1-Q3)	p value
WBC (U/L)	6.45 (4.48–8.35)	10.83 (7.96–14.24)	<0.001
Neutrophil (mmol/L)	4.01 (2.85–5.47)	7.42 (5.38–10.03)	<0.001
Lymphocyte (U/L)	1.24 (0.74–1.77)	1.09 (0.75–1.72)	0.917
Monocyte (mmol/L)	0.42 (0.28–0.74)	0.59 (0.84–1.11)	<0.001
Eosinophil (mmol/L)	0.00 (0.02–0.08)	0.00 (0.03–0.10)	0.899
RDW	40.90 (39.00–43.90)	45.15 (41.05–49.62)	0.009
MPV (fL)	10.20 (9.70–10.70)	9.97 (10.30–11.22)	0.262
MCV (fL)	80.00 (83.40–0.86.30)	88.30 (81.34–91.05)	0.003
PLT ($10^3/\mu\text{L}$)	215.00 (172.00–248.00)	225.00 (171.00–313.25)	0.283
CRP (mg/l)	40.40 (12.00–76.00)	51.35 (16.07–112.25)	0.386
LDH (U/L)	292.00 (261.00–363.00)	278.50 (231.25–396.75)	0.375
BUN (mg/dL)	29.00 (23.00–41.00)	39.00 (28.50–65.50)	0.011
TG (mg/dL)	173.00 (128.00–200.00)	120.00 (103.50–138.50)	<0.001
Procalcitonin ($\mu\text{g/L}$)	0.03 (0.05–0.14)	0.04 (0.20–0.79)	0.001
Creatinine (mg/dL)	0.83 (0.64–1.01)	0.80 (0.60–1.20)	0.709
Albumin (g/dL)	3.20 (3.60–4.03)	2.56 (3.10–3.50)	0.001
Bilirubin (mg/dL)	0.21 (0.35–0.47)	0.20 (0.30–0.60)	0.723
Uric acid (mg/dL)	3.20 (3.82–5.00)	3.75 (4.80–6.60)	0.003
NLR	3.33 (1.96–6.14)	7.32 (4.44–9.66)	0.002
PLR	171.03 (116.91–273.68)	195.89 (151.31–280.47)	0.199
MLR	0.33 (0.23–0.60)	0.66 (0.33–1.09)	0.002
CLR	27.84 (8.39–110.71)	35.47 (9.02–152.54)	0.573
LCR	0.03 (0.00–0.11)	0.02 (0.00–0.11)	0.573
LMR	2.98 (1.64–4.20)	1.49 (0.91–2.94)	0.002
NMR	7.7 6(5.98–15.05)	9.79 (6.31–15.21)	0.666
RAR	11.36 (9.90–13.84)	14.48 (10.99–17.11)	0.004
CAR	11.48 (3.03–23.51)	17.11 (6.04–37.40)	0.196
BAR	7.77 (6.49–13.12)	12.32 (8.16–23.77)	0.002
NAR	1.11 (0.76–1.73)	2.36 (1.60–3.61)	<0.001
AISI	345.55 (166.69–593.01)	1360.79 (470.19–2599.43)	<0.001
SII	650.87 (426.60–1473.50)	1484.70 (820.53–3021.69)	0.001
SIRI	1.62 (0.78–2.91)	5.47 (2.23–10.07)	<0.001
CALLY	0.11 (0.04–0.59)	0.31 (0.07–1.04)	0.097

(Continued)

Table 2 (Continued).

Characteristics	COVID-19 (n: 51) Median (Q1-Q3)	Influenza A(H1N1)(n: 38) Median (Q1-Q3)	p value
ALBI	−0.57 (−0.74– −0.51)	−0.59 (−0.71– −0.42)	0.619
HALP	25.48 (13.20–35.32)	21.36 (11.81–30.32)	0.179

Notes: Data are expressed as the median and percentiles (25%–75%), compared using Mann–Whitney *U*-test. P-value < 0.05 was considered statistically significant.

Abbreviations: WBC, white blood cell; RDW, red blood cell distribution width; MCV, mean corpuscular volume; MPV, mean platelet volume; PLT, platelets; CRP, C-reactive protein; LDH, laktat dehidrogenaz; BUN, blood urea nitrogen; TG, Triglyceride; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, lymphocyte to monocyte ratio; LCR, Lymphocyte–CRP ratio; CLR, CRP to lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio; RAR, RDW to albumin ratio; CAR, CRP to albumin ratio; BAR, BUN to albumin ratio; NAR, neutrophil to albumin ratio; AISI, aggregate index of systemic inflammation; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; CALLY, CRP-albumin-lymphocyte index; ALBI, Albumin-bilirubin skoru; HALP, albumin, lymphocyte, and platelet score.

Table 3 Comparison of Laboratory Parameters and Indices as Indicators of In-Hospital Mortality in COVID-19 and Influenza A (H1N1) Pneumonia

Characteristics	COVID-19 (n: 51) Median (Q1-Q3)			Influenza A (H1N1) (n: 38) Median (Q1-Q3)		
	Survivors (n=48)	Non-Survivors (n=3)	p	Survivors (n=33)	Non-Survivors (n=5)	p
WBC-U/L	6.20(4.41–8.31)	13.02(11.70–14.53)	0.006	10.76(7.85–14.06)	14.02(9.94–16.08)	0.218
Neutrophil-mmol/L	4.00(2.86–5.38)	8.42(5.40–12.03)	0.400	736(5.01–8.99)	14.04(6.41–18.13)	0.073
Lymphocyte-U/L	1.26(0.79–0.78)	0.27(0.17–0.49)	0.010	1.13(0.78–1.86)	0.81(0.44–1.62)	0.261
Monocyte-mmol/L	0.42(0.31–0.75)	0.20(0.15–0.33)	0.123	0.84(0.59–1.07)	0.87(0.62–3.13)	0.331
RDW	40.90(39.05–43.75)	40.70(39.70–47.20)	0.904	44.40(39.30–48.95)	49.30(45.85–57.45)	0.880
MPV-fL	10.15(9.65–10.70)	11.07(10.53–11.88)	0.143	10.20(9.95–10.60)	12.50(10.25–12.90)	0.063
MCV-fL	83.40(80.00–86.25)	84.00(82.80–85.25)	0.734	88.10(81.16–91.45)	88.50(83.40–90.85)	0.931
PLT-10 ³ /μL	222.50(177.50–248.50)	179.00(152.50–198.50)	0.215	220.00(180.00–277.00)	317.00(143.00–380.00)	0.650
CRP-mg/l	36.15(11.50–74.20)	79.40(73.10–145.20)	0.055	34.90(15.00–96.05)	110.00(47.55–130.50)	0.181
LDH-U/L	291.00(258.50–362.50)	352.00(330.50–537.00)	0.138	275.00(204.00–345.50)	480.00(366.00–1099.00)	0.013
BUN-mg/dL	28.50(22.50–38.00)	65.00 (55.50–66.50)	0.019	35.00(27.00–59.50)	80.00(46.00–108.50)	0.022
TG-mg/dL	156.00(127.00–200.00)	200.00(186.50–209.00)	0.228	120.00(101.50–135.50)	200.00(126.50–211.50)	0.030
Procalcitonin-μg/L	0.04(0.00–0.11)	0.22(0.14–1.45)	0.061	0.20 (0.04–0.53)	1.01(0.07–3.22)	0.195
Creatinine-mg/dL	0.82(0.66–1.00)	0.98(0.81–1.00)	0.645	0.78(0.55–1.03)	1.20(1.00–1.75)	0.031
Albumin-g/dL	3.60(3.20–4.06)	3.11(2.57–3.28)	0.085	3.20(2.86–3.50)	2.23(1.64–2.85)	0.012
Bilirubin-mg/dL	0.36(0.20–0.46)	0.33(0.31–0.51)	0.587	0.30(0.20–0.55)	0.42(0.30–1.49)	0.148
Uric acid-mg/dL	3.38(3.45–5.01)	3.10 (3.08–3.56)	0.200	4.80(3.60–6.55)	5.30(4.65–7.15)	0.310
NLR	2.98(1.94–5.89)	29.87(20.78–43.91)	0.010	6.85(3.91–8.52)	10.61(8.72–27.55)	0.009
PLR	162.49(116.63–251.13)	662.96(418.98–93.98)	0.049	184.61(140.43–268.55)	234.83(200.42–530.68)	0.160
MLR	0.33(0.23–0.58)	0.37(0.32–3.12)	0.057	0.66(0.32–0.99)	1.97(0.52–3.25)	0.050
CLR	27.04(8.29–5.42)	294.07(193.42–1465.78)	0.016	29.67(8.68–111.03)	164.19(36.54–238.75)	0.115
LMR	2.99(1.70–4.20)	2.70(1.43–3.15)	0.357	1.509(1.007–3.087)	0.50(0.31–1.90)	0.049
NMR	7.53(5.98–14.41)	42.10 (23.59–99.30)	0.262	9.75(6.31–14.79)	10.91(5.4–16.65)	0.914
RAR	10.91(9.90–13.53)	15.56(14.00–17.80)	0.055	13.82(10.43–15.61)	22.10(19.04–32.61)	0.001
CAR	10.02(2.97–22.80)	39.11(29.23–53.47)	0.034	11.25(6.04–33.19)	49.23(20.75–85.67)	0.045
BAR	7.47(6.47–11.56)	18.84(16.81–26.16)	0.015	10.51(7.08–20.77)	30.76(17.67–77.26)	0.013
NAR	1.10(0.75–1.65)	2.44(1.60–5.07)	0.246	2.10(1.52–2.95)	6.23(3.63–7.54)	0.004
AISI	342.46(161.18–535.95)	1037.53(666.11–2049.26)	0.128	1213.03(415.71–2092.94)	3779.57(1591.5814851.6)	0.023
SII	627.20(425.4–1208.58)	6512.75(3993.12–444.06)	0.018	1393.30(804.37–2154.93)	4202.25(2219.43–5277.85)	0.023
SIRI	0.78(1.54–2.35)	5.79(4.06–9.91)	0.034	5.03(1.72–9.35)	11.92(5.47–58.98)	0.040
CALLY	0.11(0.04–0.39)	4.60(2.69–5.45)	0.012	0.25(0.05–0.70)	1.12(0.61–3.23)	0.049

(Continued)

Table 3 (Continued).

Characteristics	COVID-19 (n: 51) Median (Q1-Q3)			Influenza A (H1N1) (n: 38) Median (Q1-Q3)		
	Survivors (n=48)	Non-Survivors (n=3)	p	Survivors (n=33)	Non-Survivors (n=5)	p
ALBI	−0.58(−0.76- −0.52)	−0.49(−0.56- −0.42)	0.215	−0.61(−0.73- −0.43)	−0.36(−0.57- −0.14)	0.029
HALP	26.09(15.98–35.60)	4.10(2.90–8.65)	0.015	24.64(12.84–32.24)	9.67(5.85–14.28)	0.012

Note: P-value < 0.05 was considered statistically significant.

Abbreviations: WBC, white blood cell; RDW, red blood cell distribution width; MCV, mean corpuscular volume; MPV, mean platelet volume; PLT, platelets; CRP, C-reactive protein; LDH, laktat dehidrogenaz; BUN, blood urea nitrogen; TG, Triglyceride; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, lymphocyte to monocyte ratio; LCR, Lymphocyte–CRP ratio; CLR, CRP to lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio; RAR, RDW to albumin ratio; CAR, CRP to albumin ratio; BAR, BUN to albumin ratio; NAR, neutrophil to albumin ratio; AISI, aggregate index of systemic inflammation; SIL, systemic immune-inflammation index; SIRI, systemic inflammation response index; CALLY, CRP-albumin–lymphocyte index; ALBI, Albumin–bilirubin skoru; HALP, albumin, lymphocyte, and platelet score.

in Model 1 and new indices derived from laboratory parameters in Model 2. Multivariate logistic regression analysis results for Model 1 and Model 2 are shown in Tables 4 and 5. In multivariate logistic regression analyses; monocytes (OR 27.327, CI 4.143–180.234, $p=0.001$), MCV (OR 1.130, CI 1.011–1.262, $p=0.031$), albumin (OR 0.314, CI

Table 4 Univariate and Multivariate Logistic Regression Analyses for Laboratory Parameters Predicting COVID-19

Univariate Logistic Regression	B	p value	OR	95% C.I.	
				Lower	Upper
Neutrophil	0.130	0.013	1.139	1.028	1.262
Monocyte	30.085	0.000	21.872	4.590	104.224
Albumin	−1.322	0.001	0.267	0.122	0.585
Uricacid	0.531	0.002	1.700	1.222	2.365
MCV	0.122	0.005	1.129	1.038	1.229
Multivariate Logistic regression	B	p value	OR	95% C.I.	
				Lower	Upper
Neutrophil	0.112	0.071	1.119	0.990	1.263
Monocyte	3.308	0.001	27.327	4.143	180.234
Albumin	−1.159	0.029	0.314	0.111	0.888
Uricacid	0.489	0.028	1.631	1.055	2.522
MCV	0.122	0.031	1.130	1.011	1.262

Note: p-value < 0.05 was considered statistically significant.

Abbreviations: MCV, mean corpuscular volume; B, Standardized regression coefficient; OR, Odds Ratio; CI, Confidence Interval.

Table 5 Univariate and Multivariate Logistic Regression Analyses for New Laboratory Indices Predicting COVID-19

Univariate Logistic regression	B	p value	OR	95% C.I.	
				Lower	Upper
LMR	−0.443	0.005	0.642	0.472	0.875
AISI	0.000	0.038	1.000	1.000	1.001
NAR	0.371	0.007	1.449	1.106	1.899
BAR	0.062	0.016	1.064	1.011	1.119
RAR	0.146	0.012	1.158	1.032	1.299

(Continued)

Table 5 (Continued).

Multivariate Logistic regression	B	P value.	OR	95% C.I.	
				Lower	Upper
LMR	−0.390	0.017	0.677	0.492	0.933
AISI	0.000	0.561	1.000	1.000	1.000
NAR	0.415	0.048	1.514	1.004	2.282
BAR	0.013	0.648	1.014	0.957	1.074
RAR	0.082	0.230	1.086	0.949	1.242

Note: P-value < 0.05 was considered statistically significant.

Abbreviations: LMR, Lymphocyte-to-monocyte ratio; AISI, aggregate index of systemic inflammation; NAR, neutrophil to albumin ratio; BAR, BUN to albumin ratio; RAR, RDW (red blood cell distribution width) to albumin ratio; B, Standardized regression coefficient; OR, Odds Ratio; CI, Confidence Interval.

0.11–0.888, $p=0.029$), and uric acid (OR 1.631, CI 1.055–2.522, $p=0.028$) were found to be significant hematologic and biochemical parameters predicting COVID-19, and LMR (OR; 0.677, CI: 0.492–0.933, $p=0.017$), and NAR (OR; 1.514, CI: 1.104–2.282, $p=0.048$) were determined as important new hematological indices predicting COVID-19.

Discussion

In this study, various haematological and biochemical parameters and indices derived from these parameters were examined in patients with COVID-19 and influenza A (H1N1) pneumonia, and easy, cheap, and accessible biomarkers that can be used for the differentiation of these two pneumonias were determined. It was shown that LMR and NAR among haematological and biochemical indices and monocytes, albumin, uric acid, and MPV among laboratory parameters were the most important parameters predicting COVID-19.

COVID-19 resulting from SARS-CoV-2, a novel coronavirus, has posed a major threat worldwide.²⁰ However, it continues to be seen all over the world, with various different clinical pictures ranging from mild cases to severe cases resulting in death.²¹ At the same time, influenza A (H1N1) virus continues to be a common disease, especially in winter and spring.²² Influenza A (H1N1) and COVID-19 pneumonia are two very different respiratory pneumonias with very similar clinical presentations and can frequently cause co-infections at the same time. Therefore, it is of great importance for clinicians to differentiate COVID-19 from other respiratory infections, including influenza. Recognition of clinical features with accurate imaging and laboratory findings can help early diagnosis of COVID-19 and prevent its spread, but the clinical, radiological, and laboratory characteristics of influenza A (H1N1) pneumonia also overlap with COVID-19.^{23,24}

Viral pneumonias caused by both species have a wide spectrum from asymptomatic infection to life-threatening and fatal.²⁵ In our study, clinical outcomes and intensive care requirements did not differ in both viral pneumonias. In the early phase of viral pneumonia, symptoms such as fever, cough, myalgia, sputum, pharyngalgia, and rhinorrhoea were found to be the most common symptoms, and gastrointestinal symptoms such as nausea and vomiting, diarrhoea, dizziness, and headache were reported to be typically added to these symptoms.²⁶ It has also been reported that shortness of breath and chest pain may occur as the disease progresses, and some COVID-19 patients may not have fever even if they have progressed to severe pneumonia. It has been shown that fever is more common in patients with influenza A (H1N1) pneumonia and gastrointestinal symptoms are more common in COVID-19 because the gastrointestinal system is the target organ of COVID-19.²⁷ In our study, fever, cough, and shortness of breath were more common in influenza A (H1N1) pneumonia, while sore throat, headache, and malaise were more common in COVID-19 pneumonia. No difference was observed between the two virus types in terms of gastrointestinal system symptoms. In terms of comorbidities, half of patients infected with COVID-19 were reported to have underlying chronic diseases such as DM, cerebrovascular and cardiovascular diseases, and in one study, it was shown to affect older adult men with chronic comorbidities more due to their poor immune function.²⁶ In our current study, age did not show a significant difference

between the two virus pneumonia types, while asthma was significantly increased in COVID-19 pneumonia, COPD was significantly increased in influenza A (H1N1) pneumonia, and CVD and DM did not differ between the two virus types.

CT examination in viral pneumonia is an important tool for differential diagnosis, follow-up, evaluation of treatment efficacy, mortality and morbidity, and the typical radiological finding for COVID-19 is ground-glass opacity with or without consolidation, specifically pure GGO²⁴ and unilateral or bilateral localization in the lower lobes.²³ However, CT imaging findings of influenza A (H1N1) pneumonia also show significant similarities.²⁸ In our study, round/nodular GGO and non-round diffuse/patchy GGO were prominent in COVID-19 pneumonia, while patchy consolidation and GGO, lobar/segmentary consolidation and micronodular/interstitial densities were prominent in influenza A (H1N1) pneumonia. Bilateral and unilateral involvement did not differ significantly in both pneumonia groups, while pleural effusion was significantly higher in influenza A (H1N1) pneumonia. Length of stay in the intensive care unit and clinical outcome (ex/survivor) did not differ in both pneumonia groups.

Among the laboratory findings, leukopenia, lymphopenia, and elevated CRP, ferritin, and D-dimer are among the most typical common laboratory tests of COVID-19, but these laboratory parameters are quite similar in both virus types.^{29,30} Because of such significant similarities between these two viruses, there is a need to identify new hematologic and biochemical indices that are easily accessible and reproducible. Hematologic indices are currently recognized as biomarkers of inflammation and clinical prognosis of viral pneumonia.^{9,31} On the other hand, new systemic inflammation markers derived from the analysis of hematologic parameters have been identified, but few studies have been conducted comparing COVID-19 with influenza by considering all of the new hematologic parameters together and focusing on epidemiologic characteristics.³² In our study, COVID-19 and influenza A (H1N1) pneumonia were compared with a wide range of hematologic parameters and new indexes. In our study, hematological parameters and hematological indices derived from hematological parameters; WBC, neutrophils, monocytes, RDW, MCV, BUN, TG, procalcitonin, albumin, uric acid, NLR, MLR, LMR, RAR, BAR, NAR, AISI, SII, SIRI showed meaningful differences between COVID-19 pneumonia and influenza A (H1N1) pneumonia. According to our univariate and multivariate logistic regression analyses, LMR and NAR among hematologic indices and MCV, monocytes, albumin, and uric acid among hematologic parameters were found to be the most important blood parameters predicting COVID-19.

Studies have shown that CBC parameters (eg NLR, LMR, NMR, PLR, NLPR, SII, AISI, and SIRI) used alone or in ratio to each other can be used as indices of inflammation and immunity in many diseases and malignancies.³³ It has also led to studies reporting significant associations between severe disease and mortality.^{34,35} NLR and PLR have been documented to be a beneficial prognostic factor for the severity of COVID-19 in various studies. Furthermore, NMR was reported to be significantly associated with pneumonia in COVID-19 patients.³⁶ In our study, NLR, PLR, and NMR were not found to be biomarkers in differentiating these two viral pneumonias. However, NLR showed a significant difference between ex and surviving patients in both viruses, indicating that it may be an important parameter in in-hospital mortality. Previous studies have demonstrated that elevated AISI, SII, and SIRI were significantly correlated with high mortality in SARS-COV-2 patients.³⁷ In the current study, SII and SIRI, which are lymphocyte-associated inflammatory indices, were not among the factors predicting COVID-19 pneumonia. However, SII and SIRI showed a significant difference between ex and surviving patients in both viruses, suggesting that it may be an indicator of in-hospital mortality.

AISI is increasingly being investigated in other disease states besides COVID-19.^{38,39} AISI has been an important determinant of disease severity and ICU admission in COVID-19 patients.⁴⁰ In our study, AISI was not a hematologic index that could distinguish COVID-19 pneumonia from influenza A (H1N1). However, it showed a significant difference in influenza A (H1N1) pneumonia in ex and surviving patients and was thought to be an important marker of mortality. CRP is an acute phase protein that responds to inflammatory cytokines. It has been suggested that CRP level reflects the severe inflammation and thus the cytokine storm associated with poor outcomes of COVID-19.⁴¹ The CLR ratio is an important marker of inflammation, especially used in bacterial infection. Recently, CLR was found to be significantly associated with COVID-19 mortality.⁴² In the current study, CRP and CLR were not found to be predictors that could distinguish these two viruses.

COVID-19 patients usually have elevated neutrophilia, leukocytosis, monocytosis, and lymphocytopenia. In our study, monocytes were higher in COVID-19 and were found to be an important predictor of COVID-19. LMR is an index

that calculates the ratio between the number of lymphocytes and monocytes obtained through routine blood samples. In general, LMR is recognized as an index or biomarker in patients with cardiac disorders due to the raised activity of monocytes, which are involved in the secretion of proinflammatory cytokines and the rupture of atherosclerotic plaques.^{43,44} In our study, low LMR was found to be an important biomarker to distinguish COVID-19 pneumonia from influenza A (H1N1) and also showed a highly significant difference compared to ex and surviving cases with influenza A (H1N1) pneumonia, indicating that it may be an important marker of in-hospital mortality.

COVID-19 disease has been shown to affect the RBC system and rheological parameters. During the acute phase of the disease, a decrease in red blood cell count, mean cellular hemoglobin concentration (MCHC), mean cellular hemoglobin (MCH), and MCV has been observed.^{45–47} Impaired RBC deformability and changes in MCV have been associated with cellular morphological changes and oxidative stress. SARS-CoV-2 virus has been suggested to invade erythroid precursors and progenitors, causing hematopoietic stress and morphologic abnormalities in RBC parameters. In addition, it has been proposed that the virus affects the cytoskeletal integrity of red blood cells by inducing membrane lipid remodeling and structural protein changes.^{46,48} During the course of COVID-19, some studies have also reported variable RBC parameters, such as increases in hemoglobin and hematocrit levels at different stages of the disease. Lin H ve guerme.^{48,49} In our study, decreased MCV was found to be one of the important parameters predicting COVID-19.

Decreased serum albumin levels have been associated with increased mortality independent of underlying diseases. It has been shown that the duration of hospital stay increased in patients with low albumin levels.^{50,51} BUN levels have also been demonstrated to be closely associated with mortality.⁴⁴ In our study, BUN showed a significant difference between ex and survivors in individuals with Influenza A (H1N1) and COVID-19 pneumonia. The relationship between low albumin levels and increased neutrophils and mortality has been investigated and NAR has been recognized as an independent predictor of mortality.⁵² In our study, albumin was found to be one of the important hematologic parameters predicting COVID-19. Among many new hematologic indices studied in the differential diagnosis of COVID-19 pneumonia, NAR was the most important index predicting COVID-19. Moreover, albumin and NAR were significantly different only in subjects with Influenza A pneumonia, between ex and survivors, and may be an index associated with in-hospital mortality.

It has been reported that malnutrition in COVID-19 patients has negative effects on the immune system, which may adversely affect prognosis. HALP score is an index used to assess the nutritional and immune systems of individual patients. In the literature, there are studies showing that a low HALP score may be recognized as a predictive index of mortality in individuals with malignancy.⁵³ The investigators also introduced CALLY index as a new combined index related to inflammation and nutritional status. The CALLY index, the CRP value is an assessment of the patient's level of inflammation, the albumin value is an indicator of liver function and nutritional status, and the lymphocyte number is an indicator of the immune system. In SARS-CoV-2 infection, lymphocyte count and albumin values decrease, and CRP values increase due to the aggravation of inflammation.⁵⁴ In our study, the HALP and CALLY indices were not considered as an important determinant in distinguishing COVID-19 pneumonia from influenza A (H1N1) pneumonia, but showed a significant difference between ex and surviving patients in determining in-hospital mortality in both COVID-19 and influenza A (H1N1) pneumonia.

Uric acid is synthesised endogenously from damaged and dead cells and exogenously in the liver, intestines, and vascular endothelium as an end product of the purine pool. Uric acid is also a dominant antioxidant in plasma and is required for the induction of type-2 immune response. With these properties, it has a protective role in infectious and neurological diseases.⁵⁵ In COVID-19 patients, symptoms and signs of the gastrointestinal and renal systems were observed in the foreground, and it was even found that renal dysfunction was associated with mortality. Kidney and GIS, which are the target organs of the virus in COVID-19 patients, are target sites for uric acid excretion. Therefore, SARS-CoV-2 infection is likely to affect uric acid metabolism and serum uric acid levels.⁵⁶

Several studies have suggested a correlation between serum uric acid levels and the severity of COVID-19.⁵⁷ Hyperuricemia is generally considered to be associated with hypoxia and systemic inflammation in respiratory diseases. Previous research (Several studies) has reported an association between high serum uric acid levels and worse outcomes of COVID-19, particularly mortality or the need for invasive mechanical ventilation.⁵⁸ On the other hand, some researchers have also reported an association between decreased serum uric acid levels and COVID-19 severity.⁵⁹

Taken together, the exact relationship between COVID-19 severity and serum uric acid levels remains unclear.⁶⁰ In our study, uric acid was found to be an important predictor in differentiating COVID-19 from influenza A (H1N1) pneumonia.

SARS-CoV-2 infection attacks the respiratory system but also central regulatory systems such as the nervous and endocrine systems, which have a fundamental function in regulating homeostasis, and significantly affects many other organs in the body and their functions. It also damages other organ systems such as the cardiovascular, gastrointestinal and urinary systems. It interacts with angiotensin-converting enzyme-2 receptors, worsening a pre-existing systemic disease or directly damaging organs.⁶¹ SARS-CoV-2 infection causes damage to many organs through possible immune mechanisms and, like many other infectious agents, causes systemic inflammation and consequent changes in some laboratory indices. In cases infected with SARS-CoV-2, biomarkers, especially those related to the coagulation system and inflammatory response, help clinicians to make a differential diagnosis and decide on possible treatments. The correct interpretation and use of biomarkers can help to understand the severity and character of inflammation and thus guide the differential diagnosis of the disease.

In our study, we evaluated the usefulness of these inflammatory indices in differentiating COVID-19 and influenza pneumonia, which have very similar clinical, radiological, and laboratory findings. We believe that we are the first study to use most of the hematological indices that have been studied separately in various studies at the same time and to use these indices together in the distinction between COVID-19 and influenza A (H1N1).

Our current study has limitations such as being a retrospective study and having a relatively small sample size. Additionally, the fact that the data were collected in late 2020, before vaccination and the full development of standardized COVID-19 treatment protocols, limits the generalizability of the mortality analysis in particular. The strength of our study was that both influenza A (H1N1) and COVID-19 pneumonias were confirmed by RT-PCR.

Conclusions

In conclusion, this study investigated various hematologic and biochemical parameters and new indices as inexpensive, easily measurable and reproducible tests for the differential diagnosis of COVID-19 and influenza A (H1N1) pneumonia and in-hospital mortality. NAR, LMR, monocytes, MCV, albumin and uric acid were shown to be the most important laboratory parameters and indices predicting COVID-19 pneumonia. Radiologically, round GGO were found to be the predominant appearance in COVID-19 compared to influenza A (H1N1) pneumonia. Hematologic parameters and new indices may be potential options for differentiating COVID-19 pneumonia from other viral pneumonias. They can guide the management of the disease and contribute to reducing mortality and morbidity, especially in cases where access to rapid diagnostic tests is limited and when the test is false-negative. More comprehensive studies involving large populations are needed for the differential diagnosis of COVID-19 and other viruses.

Data Sharing Statement

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Karamanoğlu Mehmet Bey University with the date 05.02.2025 and number 16-2025/11. The requirement for written consent was waived by the Ethics Committee of Karamanoğlu Mehmet Bey University because of the retrospective design. Patient confidentiality and data protection were rigorously protected.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors have no conflicts of interest to declare for this work.

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