First insight into eosinophils as a biomarker for the early distinction of COVID-19 from influenza A in outpatients

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Abstract. Coronavirus disease 2019 (COVID-19) and influenza A outbreaks have spread rapidly in China. It is difficult to accurately differentiate these two different respiratory tract infections on the basis of their similar early-stage symptoms and lymphocytopenia. In the present study, the age, sex and white blood cell, neutrophil, lymphocyte, monocyte and eosinophil counts, as well as the neutrophil-to-lymphocyte ratio (NLR) of 201 outpatients with confirmed COVID-19 and 246 outpatients with influenza A were investigated and compared. A receiver operating characteristic curve was drawn to determine the thresholds in distinguishing COVID-19 from influenza A Our study found that the monocyte count and NLR were significantly elevated, while the eosinophil count/percentage was higher in outpatients with COVID-19 than in those with influenza A (0.06±0.07 vs. 0.04±0.09, P=0.002; 0.95±1.12 vs. 0.56±0.95, P<0.001, respectively). Logit(P)=-1.11 + 1.29 x eosinophil percentage -12.07 x eosinophil count +1.10 x monocyte count, deduced from the eosinophil count/percentage and monocyte count, had the largest area under the curve at 0.67, with high specificity (80.1%) and a sensitivity of 47.3%. The present study demonstrated that a higher eosinophil count/percentage may be a potential biomarker to significantly differentiate early COVID-19 from influenza A.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to millions of infections and deaths worldwide since it was first reported at the end of 2019 (1). The clinical symptoms of COVID-19 are diverse and range from asymptomatic to critical illness and even fatal outcomes. With the global administration of COVID-19 vaccines, the severity and mortality of COVID-19 has markedly decreased (2). The 'dynamic COVID-zero' strategy of China has effectively maintained low morbidity and mortality rates in the country over the past 3 years (3). Reinfection may have contributed to the lower morbidity and mortality, as a survey revealed that 96.03% of reinfected individuals took medication on their own, while only 3.97% sought medical attention. No critical or hospitalized cases were found compared with the initial infection (4). During the period from December 2022 to February 2023, the prevention and control measures associated with COVID-19 were relaxed, most Chinese individuals had been infected and the reinfection incidence among primary cases increased, with only a small proportion requiring medical attention (3). Currently, the majority of infected individuals with COVID-19 are asymptomatic or have mild COVID-19. The most common symptoms in patients with COVID-19 are fever or chills, headache, muscle or body aches, dry cough, myalgia or fatigue, loss of sense of taste and rhinorrhea (5).

As SARS-CoV-2 infections continue to occur worldwide, the influenza A virus is also prevalent in China. Influenza can also be characterized by a variety of respiratory symptoms, including high fever, chills, headache, myalgia, discomfort, anorexia, cough, congestion and sore throat (6). In the early days of COVID-19, it was difficult to differentiate influenza A from COVID-19 because of the similar clinical characteristics. However, there were numerous differences between them. The age range of patients with COVID-19 was between 44 and 56 years and males were more easily infected than females (6). By contrast, the average age of patients with influenza A was 23.4 years (7) and children aged <14 years were more susceptible to influenza than COVID-19. Furthermore, 53.8% of patients with influenza were male (7). In addition, compared with patients with influenza, patients with COVID-19 had a higher incidence of chemosensory dysfunction, rash and non-productive coughs (8). However, patients with influenza had a higher prevalence of high fever, with their body temperature exceeding 41˚C within the first 24 h, compared with patients with COVID-19 (6). It was difficult to distinguish influenza

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A from COVID-19 via patient age, sex and symptoms. As the treatment regimens and prognoses differ between COVID-19 and influenza A, it is important for clinicians to accurately differentiate between these two respiratory infections on the basis of their respective characteristics in the early stages. Since the diagnostic criteria and definitions for both COVID-19 and influenza A include fever, entry screening at the fever clinic tends to start with a routine blood test and a nucleic acid PCR test. The average time of the nucleic acid PCR test to detect the virus with an instrument for PCR is 2-4 h. A routine blood test takes 10-15 min to obtain results, and every hospital can accomplish it. Therefore, if a routine blood test can help in the diagnosis of COVID-19, it may help interrupt the spread of the disease in the shortest amount of time and at the lowest cost (9,10).

Lymphopenia is commonly observed in patients with COVID-19 (5,11), SARS (12) and influenza virus infections (7,13). Although lymphopenia appears to be associated with illness severity for both influenza and COVID-19 (14), it does not appear to be a unique marker of COVID-19 and may not be useful in distinguishing viral pneumonia caused by SARS-CoV-2 and influenza virus (15). Eosinophils, a type of white blood cells, have been well-known to play an important role in combating parasitic infections (16). Recent research has found that eosinophils contribute to healthy homeostasis and have pathological roles in bacterial and viral infections, as well as certain cancers (17). A study reported that eosinopenia may be a useful biomarker for the diagnosis and prognosis of COVID-19 (18). However, to date, no study has reported that eosinopenia may be useful for the differential diagnosis of COVID-19, to the best of our knowledge. Therefore, the present study aimed to investigate the clinical significance of eosinophils in fever clinic outpatients infected with SARS-CoV-2 or influenza virus.

Patients and methods

Patients. Starting from January 2023, China has downgraded the management of COVID-19 from category A to category B (19) in accordance with the country's law on prevention and treatment of infectious disease, and removed it from quarantinable infectious disease management carried out in accordance with the Frontier Health and Quarantine Law of the People's Republic of China, in the same category as HIV and bird flu. Since February 2023, influenza A has been spreading rapidly throughout China (20), just like it is occurring in every cold season every year. To date, the epidemic of influenza A has not stopped. In the present study, fever clinic outpatients of the First Affiliated Hospital of University of South China (Hengyang, China) with confirmed COVID-19 and influenza A without any chronic underlying medical conditions were included between April 2023 and June 2023. The present study was approved by the Medical Ethical Committee of the First Affiliated Hospital of the University of South China (Hengyang, China). The diagnosis of COVID-19 was made according to the World Health Organization guidelines (21) and treatment was performed in accordance with evidence-based guidelines (22). The diagnosis and antiviral treatment of influenza A were guided by clinical practice guidelines from the Infectious Diseases Society of America and China for treating influenza in adult patients with Chinese patent medicines (23,24). All patients were newly diagnosed and did not have any other diseases, such as chronic heart or lung disease, diabetes mellitus or chronic obstructive pulmonary disease. In addition, pregnant women and minors younger than 14 years old were excluded. All outpatients at the fever clinic recruited into the present study received oral medication and did not require any further treatment. Patients who were diagnosed with COVID-19 and required hospitalization were excluded from the present study. Those outpatients who needed further treatment and were admitted to the hospital during the follow-up were also excluded from the current study. All patients enrolled in the present study were living in Hengyang (China) during the outbreak period of COVID-19 and influenza A (April 2023 to June 2023). The clinical outcomes were monitored up until the end of June 2023, which was the time-point of final follow-up.

A total of 447 outpatients, including 201 with COVID-19 [median, interquartile range (IQR), 25.0 (19.0-41.5); men/women, 112/89] and 246 with influenza A [median (IQR), 29.5 (19.0-51.0); men/women, 124/122] were randomly enrolled in the present study. Clinical data, including demographic information, medical history, exposure history, comorbidities, symptoms, signs, laboratory examinations and treatment measures, were obtained from the electronic medical record system of the First Affiliated Hospital of the University of South China. All patients developed fever ranging from 2 h to 2 days, accompanied by cough, sore throat, dizziness and fatigue, and presented to the fever clinic. Only a minority of patients received chest computed tomography scans because they had severe cough and expectoration, or the scans were requested by the patients. A total of two independent trained physicians (RH and CH) from the research team collected and verified the data from the electronic medical record system. The onset date was defined as the day when the symptoms were noticed by the patients.

Reverse transcription-quantitative (RT-q)PCR assay for SARS-CoV-2. The throat swab samples of the patients were collected for SARS-CoV-2 nucleic acid detection using a RT-qPCR assay. Nucleic acid testing was conducted at the clinical laboratory of the First Affiliated Hospital of the University of South China using the Novel Coronavirus (2019-nCoV) Dual Probes qRT-PCR Kit by Wuhan Easy Diagnosis Biomedicine Co. Ltd. with a QPT1000 real-time PCR system. Specific primers and probes for the detection of the 2019 novel coronavirus were designed on the basis of recently available data from the National Institute for Viral Disease Control and Prevention, China. The designed forward primer for Target 1 (ORF1ab gene) was 5'-CCCTGTGGGTTTTACACTTAA-3', the reverse primer was 5'-ACGATTGTGCATCAGCTGA-3' and the probe was 5'-FAM-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3'. For Target 2 (N gene), the forward primer used was 5'-GGGGAACTTCTCCTGCTAGAAT-3, the reverse primer was 5'-CAGACATTTTGCTCTCAAGCTG-3' and the probe was 5'-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3'. An aliquot of 5.0 μl of the viral RNA extract, which was extracted with the RNAeasy™ Viral RNA Isolation Kit with Spin Column (cat. no. R0035L; Beyotime Institute of Biotechnology) was mixed with 20.0 μl of a

Table I. Clinical and laboratory parameters of the enrolled outpatients with COVID-19 and influenza A in the present study.

Parameter	COVID-19 (n=201)	Influenza A (n=246)	P-value
Age, years	25.0 (19.0-41.5)	29.5 (19.0-51.0)	0.394
Men/women	112/89	124/122	0.263
WBC, x10^9/l	6.48±1.90	6.18±2.17	0.122
Neutrophil percentage	74.58±10.11	73.65±10.69	0.348
Lymphocyte percentage	14.59±9.03	16.48±9.28	0.031
Monocyte percentage	9.63±3.99	9.03±3.28	0.078
Eosinophil percentage	0.95±1.12	0.56±0.95	<0.001
Neutrophil count, x10^9/l	4.96±1.74	4.64±1.97	0.075
Lymphocyte count, x10^9/l	0.86±0.43	0.94±0.51	0.109
Monocyte count, x10^9/l	0.61±0.31	0.55±0.27	0.018
Eosinophil count, x10^9/l	0.06±0.07	0.04±0.09	0.002
NLR	7.59±5.47	6.38±4.51	0.012

Quantitative variables are presented as the mean ± SD. Age is expressed as the median (interquartile range). Categorical variables are presented as a n (%). WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; COVID-19, coronavirus disease 2019.

2019-nCoV RT-qPCR mixture according to the manufacturer's protocol. The RT-qPCR conditions were as follows: 50˚C for 15 min (RT), 95˚C for 30 sec (initial denaturation), followed by 40 cycles of 3 sec of denaturation at 95˚C and 40 sec of annealing and extension at 60˚C. The results from each sample were normalized to the internal control, 2019-nCoV RNA control. The RT-qPCR was performed in triplicate, and the mean Cq value of three independent experiments was used (25). A cycle threshold value (Ct-value) <40 for all three target genes was used to distinguish positive from negative test results.

Rapid influenza diagnostic test with antigen detection. Direct antigen detection tests in nasopharyngeal aspirates (Nanjing Synthgene Medical Technology Co., Ltd.) were used to detect the presence of influenza viruses. The detection process was carried out in strict accordance with the instruction manual of the Flu A/Flu B antigen rapid test kit (colloidal gold method).

Statistical analyses. Continuous variables are presented as the mean ± standard deviation or the median (25th percentile, 75th percentile), and categorical variables are presented as numbers (percentages). Statistical analyses of the data were performed with SPSS version 23.0 (IBM Corp.). An unpaired Student's t-test was used to compare the quantitative variables. The χ^2 test or Fisher's exact test was used to compare the categorical variables (men/women). The predictive factors for discriminating COVID-19 from influenza A, such as the white blood cell (WBC) count (x10^9/l), neutrophil percentage, lymphocyte percentage, monocyte percentage, eosinophil percentage, neutrophil count (x10^9/l), lymphocyte count (x10^9/l), monocyte count (x10^9/l), eosinophil count (x10^9/l) and neutrophil-to-lymphocyte ratio (NLR) (calculated as neutrophil counts/lymphocyte counts), were computed via univariate analysis and a multivariate logistic regression model with Cox's proportional hazards model. The diagnostic value of eosinophils and lymphocytes for distinguishing early COVID-19 from influenza A was assessed using the area under the receiver operating characteristic (ROC) curve (AUC) performed with MedCalc statistical software (version 20.0; MedCalc Software Ltd.). Cut-off points with best sensitivity and specificity were selected. Diagnostic accuracy was assessed by sensitivity, specificity, positive likelihood ratio and negative likelihood ratio. P<0.05 was considered to indicate a statistically significant difference.

Results

Demographic characteristics. A total of 447 outpatients were included in the present study, comprising 201 patients with confirmed COVID-19 and 246 patients with influenza A. The median age of the patients with COVID-19 and influenza A was 25.0 (19.0-41.5) and 29.5 (19.0-51.0) years, respectively. The percentage of men was 55.72% (112/201) and 50.41% (124/246) in the COVID-19 and influenza A group, respectively. There was no significant difference between these two groups in terms of age (P=0.394) and sex (P=0.263). Demographics and characteristics of all patients are presented in Table I.

Laboratory parameters. Laboratory testing of the patients was performed at the fever clinic (Table I). Complete blood cell counts were compared between patients with confirmed COVID-19 and those with influenza A. The lymphocyte percentage was lower in patients with confirmed COVID-19 than in those with influenza A (P=0.031); no differences with respect to lymphocyte counts (absolute count) were found between these two groups. The absolute monocyte count was significantly lower in the influenza A group compared with the confirmed COVID-19 group (P=0.018). However, patients with influenza A presented with significantly lower eosinophils (absolute count and percentage) than patients with confirmed COVID-19 (P=0.002 and P<0.001, respectively). In addition, the NLR, which is an indicator of systemic inflammation, was higher in patients with confirmed COVID-19 compared with

Table II. Univariate and multivariate logistic regression analyses of factors in discriminating coronavirus disease 2019 from influenza A.

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
WBC	1.07 (0.98-1.18)	0.123	ND	ND
Neutrophil percentage	1.01 (0.99-1.03)	0.348	ND	ND
Lymphocyte percentage	0.98 (0.96-1.00)	0.033	0.98 (0.94-1.01)	0.232
Monocytes percentage	1.045 (1.00-1.10)	0.080	ND	ND
Eosinophil percentage	1.50 (1.21-1.86)	<0.001	3.62 (1.96-6.67)	<0.001
Neutrophil count	1.10 (1.00-1.21)	0.077	ND	ND
Lymphocyte count	0.71 (0.47-1.09)	0.113	ND	ND
Monocyte count	2.23 (1.13-4.39)	0.020	3.00 (1.34-6.72)	0.008
Eosinophil count	91.14 (4.21-1974.21)	0.004	0.00 ($3.33x10^{-9}$-0.01)	0.002
NLR	1.05 (1.01-1.09)	0.012	1.04 (0.98-1.10)	0.227

HR, hazard ratio; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; ND, not determined.

Table III. AUC of factors in discriminating coronavirus disease 2019 from influenza A at the fever outpatient clinic.

Variable	AUC	95% CI	Sensitivity, %	Specificity, %	Cut-off value	+LR	-LR
Eosinophil count	0.64	0.60-0.68	41.8	79.3	<0.04x10^9/l	2.02	0.73
Eosinophil percentage	0.64	0.60-0.68	63.7	58.1	<0.30%	1.52	0.62
Monocyte count	0.55	0.50-0.60	25.9	85.0	>0.74x10^9/l	1.72	0.87
Logit(P)	0.67	0.63-0.71	47.3	80.1	>0.50	2.37	0.66

+LR, positive likelihood ratio; -LR, negative likelihood ratio; AUC, area under the receiver operating characteristic curve.

those with influenza A (P=0.012). There were no significant differences in the WBC count or neutrophils (P>0.05). The detailed information is shown in Table I.

Treatment and clinical outcomes. Both groups of patients received therapy according to the aforementioned clinical practice guidelines; they received antiviral therapy (Azvudine prescribed for COVID-19 at 5 mg once a day for 5 days; Oseltamivir for influenza A at 75 mg twice a day for 5 days; Baloxavir for influenza A at 40 mg 1 dose), antipyretic medication (acetaminophen or salicylates) and Chinese patent drugs (Lianhua Qingwen granule, three capsules three times a day for 5 days). As of the final date of follow-up, only one patient with confirmed COVID-19 required admission to the hospital to receive oxygen therapy and respiratory support, and no patient died. On the other hand, none of the patients with influenza A were hospitalized.

Univariate and multivariate analyses of factors for discriminating COVID-19 from influenza A. Logistic regression analysis was performed to identify which clinical parameters were able to discriminate COVID-19 from influenza A. As shown in Table II, the lymphocyte percentage (P=0.033), eosinophil percentage (P<0.001), monocyte count (P=0.020), eosinophil count (P=0.004) and NLR (P=0.012) were able to distinguish COVID-19 from influenza A in the univariate analysis. According to the multivariate analysis,

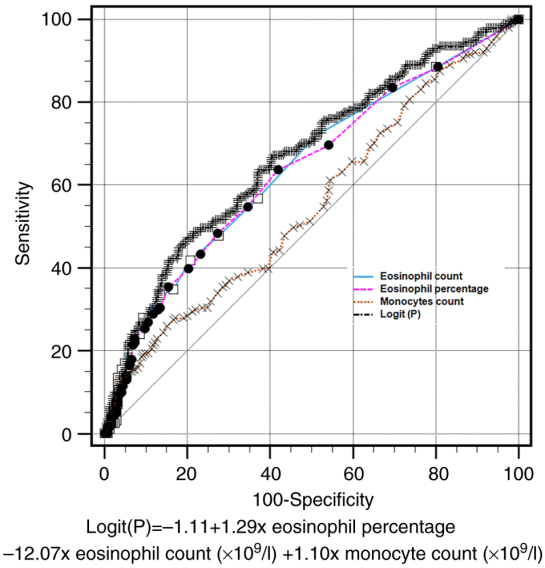

Figure 1. Receiver operating characteristic curve indicating that eosinophils may serve as a potential biomarker for the early distinction of coronavirus disease 2019 from influenza A in outpatients.

the eosinophil percentage [hazard ratio (HR), 3.62; 95% CI, 1.96-6.67; P<0.001], eosinophil count (HR, 0.00; 95% CI, $3.33x10^{-9}$-0.01; P=0.002) and monocyte count (HR, 3.00; 95% CI, 1.34-6.72; P=0.008) were the independent risk factors for the early distinction of COVID-19 from influenza A among outpatients. The results are presented in Table II.

Eosinophils as a biomarker for the early distinction of COVID-19 from influenza A in outpatients. A ROC curve of combined parameters was constructed to discriminate between COVID-19 and influenza A among the outpatients. According to the multivariate analysis results, a new parameter was deduced, which was automatically generated by MedCalc statistical software (version 20.0): Logit(P)=-1.11 + 1.29 x eosinophil percentage -12.07 x eosinophil count ($x10^9$/l) + 1.10 x monocyte count ($x10^9$/l). The eosinophil count, with a cut-off value <$0.04x10^9$/l, had a sensitivity of 41.8%, specificity of 79.3%, positive likelihood ratio of 2.02 and negative likelihood ratio of 0.73. The AUC was 0.64 [standard error (SE)=0.03; 95% confidence interval (CI), 0.60-0.68]. The AUC of the eosinophil percentage (cut-off value <0.30%) was 0.64 (SE=0.03; 95% CI, 0.60-0.68), that of the monocyte count (cut-off value >0.74 $x10^9$/l) was 0.55 (SE=0.03; 95% CI, 0.50-0.60) and that the AUC of the Logit(P) (cut-off value >0.50) was 0.67 (SE=0.03; 95% CI, 0.63-0.71). No significant differences associated with the AUC were found among the eosinophil percentage, eosinophil count or Logit(P). However, compared with the monocyte count, the AUC of the eosinophil percentage, eosinophil count and Logit(P) were significantly higher (P=0.028, P=0.012 and P<0.001, respectively; results shown in Table SI). These results indicate that eosinophils may serve as a potential biomarker to help physicians distinguish COVID-19 from influenza A in fever clinics. These results are presented in Table III and Fig. 1.

Discussion

COVID-19 and influenza A have numerous similarities and differ in several aspects. For instance, COVID-19 show mild upper respiratory symptom similar to the common cold in early stages (26), nonproductive cough and shortness of breath are relatively large (27); high fever and cough is the common symptom of influenza (7). Besides, other clinical symptoms, including fever, chemical sensory disturbance, damage to the reproductive system, constitutional symptoms and rash, were developed in COVID-19 (28); hyperthermia, photophobia and conjunctivitis was caused by influenza A (6).

But the mortality rate of COVID-19 is higher than that of influenza A; thus, clinicians and epidemiologists should differentiate between them as early as possible. Blood cell count analysis is a simple, effective and rapid laboratory test that has been widely used in clinical practice. Although hematological parameters associated with lymphocytopenia in patients with influenza and COVID-19 are similar, the situation is different regarding eosinophils: Patients with confirmed COVID-19 presented with small but significantly increased eosinophil counts than those with influenza A, which may help distinguish COVID-19 from influenza A in a short amount of time. This insight may be helpful for identifying factors that may aid in making a definitive diagnosis.

Eosinophils are white blood cells that play a homeostatic role in the body's immune response and are involved in combating various parasitic, bacterial and viral infections, as well as certain cancers (17). It has been indicated that human eosinophils contribute to viral clearance (29) and are present in patients with moderate-to-severe COVID-19 (30). Eosinophil counts have been used in several algorithms to predict the severity of COVID-19. Eosinopenia is a presenting sign of SARS-CoV-2 infection, and an association between eosinopenia and disease severity has been reported (18). Low peripheral eosinophil counts returned to normal levels when patients recovered from severe COVID-19 (31). The value of peripheral blood eosinophil counts at patient presentation has been examined for its ability to distinguish between COVID-19 and influenza virus infection. Compared with that of patients with influenza A, the mean eosinophil count was significantly increased in patients with COVID-19 Univariate and multivariate logistic regression analyses were also performed. The results suggested that an eosinophil count <$0.04x10^9$/l or eosinophil percentage <0.3% and a clear epidemiological exposure history are primary significant factors that distinguish COVID-19 from influenza A. The role of eosinophils in antiviral responses in the pathophysiology of COVID-19 remains to be elucidated. Additional studies are needed to uncover the interplay of eosinophils with coronavirus and influenza virus.

In the present study, it was found that the monocyte count was significantly higher in patients with COVID-19 compared with patients with influenza A. However, when the ROC curve was used to calculate the AUC, the AUC for monocytes was lower than that for the eosinophil percentage, eosinophil count and Logit(P).

The NLR is an indicator of the systematic inflammatory response and is used to predict the prognosis of patients with viral pneumonia (32). An elevated NLR was associated with COVID-19 progression and the return to normal levels may be associated with improved prognosis (32). The present findings indicate that an elevated NLR level may be beneficial for the early distinction of COVID-19 from influenza A, but it is not of greater value than the eosinophil percentage and eosinophil count.

There are several limitations to the present study. First, the data were obtained from a single clinical research center, and the conclusion of the present study should be validated in a multicenter, large-scale cohort. Furthermore, the experimental data are limited. The participants enrolled were newly diagnosed with COVID-19 and influenza A from epidemic seasons in the fever clinic. General information, such as the lifestyles, family history, smoking or smoking environment history of the patients, was not collected, and these factors may affect the conclusions as potential confounding factors. The relatively small sample size may affect the accuracy of the conclusions. Furthermore, the outpatients included in the present study had mild conditions, not moderate or severe conditions, and the progression of mild-to-moderate or severe illness was not evaluated. In most cases, the symptoms gradually alleviate after 2-3 days. When the patients were contacted by phone, they did not accept any follow-up. Therefore, the present study investigated only a single blood count test. Finally, the present study only focused on the count and percentage of eosinophils

and monocytes from a regular blood test, and further research should be conducted to explore the phenotype of eosinophils, monocytes and other blood cells, such as the cytokine levels secreted by these cells, granzyme B, perforin and T-cell subpopulations. These findings will offer promising guidelines for further experimental and clinical studies to distinguish between COVID-19 and influenza A.

In conclusion, the present study revealed that the monocyte count and NLR were significantly higher and that the eosinophil count/percentage was higher in outpatients with COVID-19 compared with those with influenza A from a fever clinic. These features may help significantly differentiate early COVID-19 from influenza A.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CC performed the experiments, analysed the data and edited the manuscript. HX checked and confirmed the authenticity of the raw data and analysed the data. RG collected clinical and laboratory parameters of every enrolled patient and interpreted data for this work. CD designed and complemented this work and reviewed the manuscript. JT designed the present study, solved related questions and approved the final version to be published. CD and JT confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Medical Ethical Committee of the First Affiliated Hospital of the University of South China (Hengyang, China; approval no. 2023110103002). The requirement for informed consent was waived for this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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