Lymphocyte monocyte ratio is an effective and simple predictor for nosocomial influenza outbreaks

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Abstract

Objectives

Nosocomial influenza outbreak detection remains challenging. We evaluated the diagnostic utility of blood cell parameters, along with their capacity to differentiate between hospital acquired influenza and coronavirus disease 2019 (COVID-19).

Methods

We retrospectively analyzed patients diagnosed with nosocomial influenza from January 2017 to December 2019, and patients with COVID-19 in early 2020 at a tertiary teaching hospital in Beijing, China. We compared the differences between blood cell count and ratios (lymphocyte-to-monocyte ratio [LMR], neutrophil-to-lymphocyte ratio [NLR], lymphocyte-to-platelet ratio [LPR]) at symptom onset, before (admission), and after (recovery) nosocomial influenza. We also compared the abovementioned parameters between influenza and COVID-19 patients.

Results

Lymphocyte count, LMR, and LPR were significantly lower in the symptom onset than in the admission and recovery groups ($p < 0.001$), while NLR was higher ($p < 0.001$). LMR and NLR exhibited similar and consistent tendencies among different subgroups of patients with nosocomial influenza ($p < 0.001$). The area under the receiver operating curve (AUC) of LMR, NLR, LPR, and lymphocyte count were 0.914, 0.872, 0.806, and 0.866, respectively. The optimal LMR cut-off value was 2.50, with specificity and sensitivity of 92.0% and 81.3%, respectively. Peripheral blood cell ratios can help diagnose nosocomial influenza significantly earlier than conventional methods. For differentiating influenza and COVID-19, the AUCs of LMR was 0.825.

Conclusions

LMR effectively predicts nosocomial influenza outbreaks, particularly during the COVID-19 pandemic when simultaneous transmission can be a substantial threat.

Introduction

Influenza is an infectious respiratory disease which is characterized by annual seasonal epidemics.¹ The World Health Organization has estimated that each year, approximately one billion people are infected, and as many as 500,000 people die from influenza worldwide, with the very young (< 1 year) and elderly (> 65 years) individuals being the most vulnerable groups. Other risk factors for severe disease or death include underlying pulmonary or cardiac conditions, diabetes mellitus, or immunocompromising conditions.² Pregnancy and obesity are also recognized as risk factors for severe influenza. The main strains circulating in humans include influenza A (H1N1) pdm09, influenza A (H3N2), and influenza B (B/Yamagata and B/Victoria).³

Nosocomial influenza is an emerging issue that is gaining increased recognition.⁴⁻⁶ Outbreaks of hospital-acquired influenza can occur in all types of hospital wards, with considerable consequences for both the patients and hospitals. However, the detection of nosocomial influenza cases and outbreaks is difficult and non-ideal because of the non-specific symptoms and signs of the disease, as well as the low availability and high cost of diagnostic tests. Recommended diagnostic methods for influenza include polymerase chain reaction (PCR), antigen detection, and viral culture. Although PCR tests are highly sensitive,⁷ they are expensive, require specialized equipment and personnel, and have a long turnaround time. Therefore, discovery of other reliable surrogate markers is necessary.

Peripheral blood leucocyte ratios derived from the complete blood count, mainly lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR), have been investigated in many diseases,^{8–11} including respiratory viral infections such as influenza.¹² It was reported that an LMR < 2 could be an effective marker to predict influenza in emergency rooms and hospitalized patients.¹³ However, whether these ratios are effective in predicting nosocomial influenza outbreaks remains to be investigated. The coronavirus disease 2019 (COVID-19) pandemic has swept throughout the world and has captured our attention. As of July 11, 2021, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected more than 200 countries, resulting in more than 186 million identified cases with more than 4 million confirmed deaths.¹⁴ Both influenza and COVID-19 are viral diseases that affect the respiratory tract first and have a similar presentation; simultaneous transmission of COVID-19 and influenza is a concern, and appropriate biomarkers to differentiate them are of great value.

This study retrospectively analyzed leukocytes and their ratios among patients with hospital-acquired influenza, evaluated the diagnostic utility of blood cell ratios (LMR; NLR; lymphocyte-to-platelet ratio, LPR), and aimed to find a suitable marker for the rapid diagnosis of nosocomial influenza outbreaks. We also analyzed the abovementioned markers among COVID-19 patients to evaluate their capacity to differentiate between COVID-19 and influenza.

Patients And Methods

We collected data from the Nosocomial Infection Surveillance System (NISS) of Peking Union Medical College Hospital (PUMCH), a large tertiary academic hospital in Beijing, China, from January 2017 to December 2019. Data included demographic and clinical characteristics, complete blood count (CBC), tests for influenza A/B, and turnaround time of the tests.

We applied the following inclusion criteria to the patients: 1) inpatients who had at least two of the following symptoms: fever, cough, runny nose, muscle soreness, fatigue, and sore throat; 2) symptom onset $\geq$ 48 hours after admission; 3) inpatients from surgical and medical wards with $\geq$ 8 identified cases during a short period; 4) a positive antigen test and/or PCR for influenza A/B; and 5) patients considered epidemiologically correlated in the same ward by an infection control officer. All cases were reviewed by the authors, and cases that were likely to be community-acquired or sporadic were excluded. Patients with incomplete data and those from the emergency room or intensive care unit were also excluded.

The parameters derived from CBC were recorded and analyzed at three time points: admission, onset of influenza symptoms, and recovery or discharge. CBC tests were conducted using a CELL DYN 3700 hematology analyzer. All patients were diagnosed by PCR or antigen testing using throat swab specimens during hospitalization. The return times of CBC and influenza tests were also recorded. Demographic characteristics and clinical data collected included sex, age, admission department, time of symptom onset, days in hospital, symptoms and signs, maximum body temperature, and underlying conditions. Clinical assessment and outcomes, as well as LMR and NLR were collected and calculated at all three time points, which were labeled as admission, symptom onset, and recovery (Table 1).

Table 1
Patient characteristics

Characteristics	Influenza group (n = 112)	COVID-19 group (n = 22)
Male sex-no. (%)	46 (41.1%)	13 (59.1%)
Age-years		
Mean	54.55 ± 19.04	44.36 ± 17.91
Range	17–101	6–69
Department-no. (%)		
Obstetrics and Gynecology	9(8.0%)	
Orthopedics	13(11.6%)	
General surgery	8(7.1%)	
Respiratory	31(27.7%)	
Immunology	18(16.1%)	
Nephrology	21(18.8%)	
Cardiology	12(10.7%)	
Cases of year-no. (%)		
2017/01-2017/12	34(30.4%)	
2018/01-2018/12	42(37.5%)	
2019/01-2019/12	36(32.1%)	
Days of hospitalization	13 (7,24)	
Lag time between symptom onset and diagnosis-hour	32.63 (19.24,53.72)	
Lag time between symptom onset to CBC-hour	3.51 (1.85,16.30)	
Time between CBC and diagnosis-hour	25.63 (11.13,41.79)	
Symptom onset to recovery or discharge	51.63 (28.50,95.00)	
Clinical symptoms-no. (%)		
Fever	110(98.2%)	18 (81.8%)
Cough	76(67.9%)	12 (54.5%)
Sputum	56(50.0%)	3 (13.6%)
Sore throat	35(31.3%)	5 (22.7%)
Headache	7(6.3%)	1 (4.5%)
Fatigue	14(12.5%)	6 (27.3%)
Muscle soreness	4(3.6%)	1 (4.5%)
Runny nose	16(14.3%)	3 (13.6%)
Maximum body temperature -°C	38.7 ± 0.7	38.0 ± 0.5

Characteristics	Influenza group (n = 112)	COVID-19 group (n = 22)
Underlying diseases-no. (%)		
Hypertension	30(26.8%)	1 (4.5%)
Type II diabetes	9(8.0%)	1 (4.5%)
Diagnostic measure-no. (%)		
Antigen	30(26.8%)	
Nucleic acid	84(75.0%)	
Types of influenza-no. (%)		
Influenza A	100(89.3%)	
Influenza B	12(10.7%)	
Tamiflu treatment-no. (%)	93(83.0%)	

We chose all patients diagnosed with COVID-19 at PUMCH in early 2020 as the COVID-19 group. They visited the fever clinic in the early stage shortly after the onset of symptoms (e.g., fever). Demographic characteristics, clinical data, and CBC parameters upon their visit to the fever clinic were recorded and analyzed.

Statistical analysis

Normally distributed continuous variables were expressed as means $\pm$ standard deviation ($X \pm SD$), non-normally distributed continuous variables were expressed as medians (interquartile range), and categorical variables were expressed as frequencies (composition ratio). The independent sample *t*-test was used for comparing normally distributed continuous variables between groups, the *Mann-Whitney U* test was used for comparison of non-normally distributed continuous variables between groups, and the chi-square test was used for categorical variables. *Statistical significance was set at $p < 0.05$* . All data were analyzed using SPSS 25.0 (SPSS, Inc, Chicago, IL).

Results

3.1 Clinical characteristics of patients with nosocomial influenza and COVID-19

We enrolled 112 patients with nosocomial influenza and 22 with COVID-19. The influenza group came from seven wards, including nine (8.0%) from the obstetrics and gynecology ward, 13 (11.6%) from the orthopedic ward, eight (7.1%) from the general surgery ward, 31 (27.7%) from the pulmonary ward, 18 (16.1%) from the rheumatology ward, 21 (18.8%) from the nephrology ward, and 12 (10.7%) from the cardiology ward. Among them, 46 patients (41.1%) were men, with a mean age of 54.55 ± 19.04 years. Thirty-four (30.4%), 42 (37.5%), and 36 (32.1%) patients were included in 2017, 2018, and 2019, respectively. Fever was the most common symptom (n = 110, 98.2%), with a maximum body temperature of $38.7^\circ\text{C} \pm 0.7^\circ\text{C}$. Cough (n = 76, 67.9%), sputum (n = 56, 50.0%), sore throat (n = 35, 31.3%), runny nose (n = 16, 14.3%), and fatigue (n = 14, 12.5%) were also common. A large proportion of patients (84; 75.0%) demonstrated positive nucleic acid test results for influenza, while 30 (26.8%) had positive antigen test results. The number of patients with influenza A and influenza B was 100 (89.3%) and 12 (10.7%), respectively.

In the COVID-19 group, 13 (59.1%) patients were men, with a mean age of 44.36 ± 17.9 years, which was significantly lower than that in the influenza group ($p = 0.033$). The most common symptom was fever (n = 18, 81.8%), with a

maximum body temperature of $38.0 \pm 0.5^{\circ}\text{C}$. Similar to influenza, cough ($n = 12$, 54.5%), fatigue ($n = 6$, 27.3%), sore throat ($n = 5$, 22.7%), sputum ($n = 3$, 13.6%), and runny nose ($n = 3$, 13.6%) were frequently observed (Table 1).

3.2 Lymphocyte count, LMR, and LPR were significantly lower, while NLR was higher among patients with nosocomial influenza

Lymphocyte count, LMR, and LPR all decreased with the onset of influenza symptoms such as fever, and returned to the previous level when symptoms resolved several days later. During this course, neutrophil and monocyte levels as well as the NLR increased, whereas white blood cell count (WBC) showed no significant elevation. At symptom onset, the values of LMR, NLR, and LPR ($\times 10^{-2}$) were 1.58 (1.23, 2.19), 7.37 (4.83, 12.14), and 0.38 (0.25, 0.56), respectively, and all were statistically significant compared to those on admission (Table 2). The tendencies of the three ratios are shown in Fig. 1. The decrease in LMR from admission to symptom onset was significant.

Table 2
Laboratory findings of the participants.

Characteristic	Admission group($n = 112$)	Symptom Onset group($n = 112$)	Recovery group($n = 112$)	COVID-19 group ($n = 22$)	P1 value	P2 value	P3 value
WBC ($\times 10^9/\text{L}$)	6.79(5.36,8.84)	6.94(5.34,9.99)	6.39(5.03,7.90)	5.11 (4.07,5.88)	0.989	0.166	< 0.001
Neutrophil ($\times 10^9/\text{L}$)	4.52(3.38,6.27)	5.48(4.17,8.08)	4.23(2.90,5.40)	3.05(2.08,4.50)	0.009	< 0.001	< 0.001
Lymphocyte ($\times 10^9/\text{L}$)	1.57(1.12,2.03)	0.74(0.52,1.02)	1.49(1.19,2.10)	1.33(1.07,1.61)	< 0.001	< 0.001	< 0.001
Monocyte ($\times 10^9/\text{L}$)	0.37(0.29,0.48)	0.44(0.34,0.57)	0.38(0.29,0.47)	0.36(0.25,0.52)	0.056	0.015	0.293
Platelet ($\times 10^9/\text{L}$)	228(175,296)	189(145,252)	210(151,285)	195(154,259)	0.022	0.317	0.949
LMR	3.89(2.66,5.21)	1.58(1.23,2.19)	3.85(2.96,5.66)	3.69(2.76,5.44)	< 0.001	< 0.001	< 0.001
NLR	2.75(1.92,4.76)	7.37(4.83,12.14)	2.65(1.62,3.88)	2.16(1.35,3.73)	< 0.001	< 0.001	< 0.001
LPR($\times 10^{-2}$)	0.67(0.45,0.96)	0.38(0.25,0.56)	0.73(0.56,1.03)	0.76 (0.48,1.0)	< 0.001	< 0.001	< 0.001
P1 value is the p value of Admission group and Symptom Onset group.							

P2 value is the p value of Recovery group and Symptom Onset group.

P3 value is the p value of Symptom Onset group and COVID-19 group.

3.3 Changes in LMR and NLR were consistent in different subgroups

LMR and NLR showed a similar and consistent tendency among different subgroups of patients with nosocomial influenza. Both ratios demonstrated significant changes compared to the baseline, followed by recovery to previous levels in both medical (respiratory, rheumatology, nephrology, and cardiology) and surgical (obstetrics and gynecology, orthopedics, and general surgery) patients infected with both influenza A and influenza B virus types, as well as in patient groups of different years ($p < 0.001$) (Tables 2, 3, and 4).

Table 3
LMR under different groups

LMR	Admission group	Symptom Onset group	Recovery group	P1 value	P2 value
Internal medicine groups(n = 82)	3.44(2.57,5.09)	1.58(1.24,2.30)	3.78(2.78,5.31)	< 0.001	< 0.001
Surgery groups(n = 30)	4.56(3.79,5.49)	1.57(1.12,2.15)	4.96(3.48,6.83)	< 0.001	< 0.001
Influenza A groups(n = 100)	3.89(2.74,5.21)	1.56(1.20,2.19)	3.93(3.00,5.68)	< 0.001	< 0.001
Influenza B groups(n = 12)	3.90(2.49,5.74)	1.76(1.40,2.36)	3.43(2.75,4.50)	< 0.001	< 0.001
2017 groups(n = 34)	3.47(2.56,4.70)	1.49(1.13,1.92)	3.46(2.68,5.04)	< 0.001	< 0.001
2018 groups(n = 42)	4.25(2.71,5.40)	1.69(1.40,2.31)	3.98(3.32,6.76)	< 0.001	< 0.001
2019 groups(n = 36)	3.71(2.67,5.53)	1.47(1.13,2.18)	4.12(3.30,5.87)	< 0.001	< 0.001
<i>P1 value is the p value of Admission group and Symptom Onset group.</i>					

P2 value is the p value of Recovery group and Symptom Onset group.

The 2017, 2018 and 2019 groups labeled nosocomial influenza cases diagnosed in 2017, 2018 and 2019, respectively.

Table 4
NLR under different groups

NLR	Admission group	Symptom Onset group	Recovery group	P1 value	P2 value
Internal medicine groups(n = 82)	3.09(2.06,5.09)	7.27 (4.56, 12.60)	2.72(1.57,4.55)	< 0.001	< 0.001
Surgery groups(n = 30)	2.30(1.74,3.13)	8.06(5.52,10.24)	2.32(1.66,3.04)	< 0.001	< 0.001
Influenza A groups(n = 100)	2.86(1.94,4.87)	8.05(4.96,12.18)	2.65(1.62,4.14)	< 0.001	< 0.001
Influenza B groups(n = 12)	2.35(1.88,3.83)	5.50(4.45,10.70)	2.14(1.60,3.32)	< 0.001	< 0.001
2017 groups(n = 34)	3.18(2.16,4.59)	7.35(4.61,13.76)	2.62(1.61,4.73)	< 0.001	< 0.001
2018 groups(n = 42)	2.48(1.90,4.73)	6.65(4.80,10.13)	2.64(1.57,5.00)	< 0.001	< 0.001
2019 groups(n = 36)	3.08(1.70,5.05)	8.25(5.49,13.59)	2.72(1.62,3.48)	< 0.001	< 0.001
<i>P1 value is the p value of Admission group and Symptom Onset group.</i>					
<i>P2 value is the p value of Recovery group and Symptom Onset group.</i>					
<i>The 2017, 2018 and 2019 groups labeled nosocomial influenza cases diagnosed in 2017, 2018 and 2019, respectively.</i>					

We applied receiver operating characteristic (ROC) curve analysis to evaluate the diagnostic value of the abovementioned blood cell count and ratios; the parameters on recovery were used as the control group. The area under the curve (AUC) values of LMR, NLR, LPR, and lymphocyte count were 0.914 (95% confidence interval [CI]: 0.874–0.954), 0.872 (95% CI: 0.825–0.920), 0.806 (95% CI: 0.749–0.864) and 0.866 (95% CI: 0.817–0.915), respectively. LMR had the highest AUC among NLR, LPR, and lymphocytes. The optimal cutoff value for LMR was 2.50. The specificity and sensitivity were 92.0% and 81.3%, respectively. The optimal cutoff value for NLR was 3.89. The specificity and sensitivity were 75.9% and 87.5%, respectively (Fig. 1, 2 – 1,2–2 and Table 5). The absolute change in LPR was much smaller than that in LMR and NLR.

Table 5
ROC curve was used to evaluate the diagnostic value for influenza.

	AUC	CI 95%	P value	Optimal cut off value	Specificity	Sensitivity
LMR	0.914	0.874–0.954	< 0.001	2.5049	0.920	0.813
NLR	0.872	0.825–0.920	< 0.001	3.8947	0.759	0.875
LPR	0.806	0.749–0.864	< 0.001	0.005221	0.786	0.732
Lymphocyte ($\times 10^9/L$)	0.866	0.817–0.915	< 0.001	1.235	0.732	0.884
<i>ROC curve was obtained by comparing Symptom Onset group with Recovery group.</i>						

3.4. LMR and NLR can differentiate influenza from COVID-19

Compared to the COVID-19 group, the nosocomial influenza group showed reduced lymphocyte count and elevated WBC and neutrophil counts ($p < 0.001$). Monocyte and platelet levels demonstrated no statistically significant differences. The values of LMR, NLR, and LPR ($\times 10^{-2}$) in the COVID-19 group were 3.69 (2.76, 5.44), 2.16 (1.35, 3.73), and 0.76 (0.48, 1.0), respectively.

We also performed ROC curve analysis to assess the value of LMR, NLR, and LPR in discriminating influenza from COVID-19. The AUC values for LMR, NLR, and LPR were 0.825 (95% CI: 0.715–0.936), 0.871 (95% CI: 0.777–0.964), and 0.780 (95% CI: 0.673–0.887), respectively. LMR and NLR had higher AUC values compared to LPR. The optimal cutoff value for LMR was 2.642. The specificity and sensitivity were 81.8% and 83.0%, respectively. The optimal cutoff value for NLR was 3.567. The specificity and sensitivity were 77.3% and 90.2%, respectively (Tables 2, 6 and Fig. 3).

Table 6
ROC curve was used to evaluate the diagnostic value between influenza and COVID-19.

	AUC	CI 95%	P value	Optimal cut off value	Specificity	Sensitivity
LMR	0.825	0.715–0.936	< 0.001	2.642	0.818	0.830
NLR	0.871	0.777–0.964	< 0.001	3.567	0.773	0.902
LPR	0.780	0.673–0.887	< 0.001	0.00535	0.727	0.741

3.5. LMR is a faster and cost-efficient method for the detection of nosocomial influenza

Peripheral blood cell ratios can help in establishing the diagnosis of nosocomial influenza significantly earlier than PCR or antigen testing ($p < 0.001$). The average time gap from the onset of symptoms (mostly fever) to CBC test was 3.51 (1.85,16.30) hours, whereas the time gap between symptom onset to a positive PCR or antigen test was 32.63

(19.24,53.72) hours, which is more than one day longer. In addition, for this group of patients, the total hospital stay was 13 (7,24) days, and time interval from symptom onset to recovery or discharge was 51.63 (28.50, 95.00) hours (Table 1).

LMR is also a cost-efficient diagnostic tool. The net charge of a CBC test in PUMC Hospital is 20 Yuan (about 3 dollars), while the price is 120 Yuan (about 18 dollars) for a PCR test and 60 Yuan (about 9 dollars) for an antigen test.

Discussion

Influenza remains an important disease despite the COVID-19 pandemic. Given the fact that COVID-19 is likely to be a long-term threat, simultaneous transmission of both diseases during the flu season continues to be a great concern. Nosocomial influenza jeopardizes the normal functioning of the hospital system, endangers the health of the inpatients with underlying comorbidities, and increases the risk of infection to the medical staff. Although nuclear acid testing using PCR is a reliable diagnostic tool, it requires adequate resources and has a long turnaround time.

CBC is a fast and convenient test that offers valuable information about the differential concentration of various blood cells as well as the ratios of certain cell components. It is a routine test conducted for newly admitted patients or those with a sudden onset of fever in daily practice in our center. This study revealed a clear two-way curve when LMR, NLR, and PLR were calculated and compared between the time points of admission, influenza symptom onset, and recovery. In ROC curve analysis, all three ratios showed large AUC values, along with relatively high sensitivity and specificity; however, LMR is the preferred indicator for influenza diagnosis for the following reasons: first, it involves two remarkably changed parameters (lymphocytes and monocytes); second, the specificity is higher than NLR and LPR; third, although not shown in the present study, previous studies have reported that NLR is significantly elevated among COVID-19 patients and can predict their outcome.^{15–17} The reduction in LMR is universal regardless of the patients' sex, age, or underlying diseases. There was no significant difference in LMR levels between different influenza types, years, or wards (surgical vs. medical). Notably, our study shows that parameters such as LMR can save more than one day in the diagnosis of influenza with a much cheaper price, which is a remarkable advantage in the context of nosocomial influenza detection and prevention.

Studies using lymphocyte count and leukocyte ratios for influenza diagnosis date back to the H1N1 pandemic in 2009.¹⁸ A lymphocyte to monocyte ratio below 2 was proposed as a screening tool for influenza. Zheng et al¹³ described a series of 15 cases of PCR-proven influenza-infected hospitalized adult patients, of whom 80.0% had an LMR of < 2 and 93.3% had an LMR < 2.5 at the point of influenza diagnosis. McClain et al. measured LMR daily in patients experimentally infected with influenza H3N2 (n = 17), respiratory syncytial virus (RSV, n = 20), and human rhinovirus (HRV, n = 20).¹⁹ LMR < 2 predicted 100% of all symptomatic influenza-infected patients on day 3 with peak symptom severity, but was less predictive for symptomatic RSV (60%) or HRV (18%). Another study compared LMR in patients in the emergency department diagnosed with H1N1 influenza (n = 18) or culture-proven *Streptococcus pneumoniae* community-acquired pneumonia (CAP; n = 18) and found that LMR < 2 was associated with influenza (67% vs. 38%, p = 0.05). Yuan et al. al²⁰ evaluated the application of neutrophil-lymphocyte ratio in the diagnosis of influenza among preschool children, and found that among 378 children with an influenza-like illness, 99 (26.19%) cases were positive for influenza A. Furthermore, there was a significant difference in the NLR between patients with influenza A infection and children without infection (p < 0.05). When NLR was 0.42, the sensitivity for the prognosis was 86.1%, specificity was 93.2%, and AUC was 0.594.

A decrease in LMR can result from lymphopenia and/or monocytosis.²¹ Previously, relative lymphopenia was found to be an early and reliable laboratory finding in adult influenza A.^{22,23} Cunha et al. claimed that, similar to human seasonal influenza A, relative lymphopenia appears to be a laboratory marker of H1N1.²² However, the exact mechanism remains to be elucidated. Dynamic changes in the lymphocyte count in adult patients with severe pandemic H1N1 influenza A

were also observed.²⁴ Lymphocyte proportions and absolute counts returned to normal or remained slightly higher than normal within 2–3 weeks after disease onset. Lymphopenia may be associated with apoptosis induced by viral infection.²⁵ Lymphopenia may also result from the redistribution and migration of lymphocytes to the respiratory system to combat the virus.²⁴ There is evidence that influenza virus infection could induce apoptosis of lymphocytes and temporally destroy this line of defense of the immune system.²⁶ Analysis of lymphocyte subpopulations after exposure to influenza A virus showed that a portion of the CD3⁺, CD4⁺, CD8⁺, and CD19⁺ lymphocytes became apoptotic.²⁷ Lymphocyte apoptosis likely represents part of an overall beneficial immune response but could also be a possible mechanism of disease pathogenesis. Recruitment of monocytes is essential for the effective control and clearance of viral infections, including influenza.²⁸ Monocytes egress from the bone marrow into the circulation mediated by CC-chemokine receptor 2 (CCR2). It has been shown that the increase in circulating monocytes that is associated with infection or sterile inflammation is mediated by CCL2 (CC ligand 2, also known as MCP1) and CCL7 (MCP3), triggering CCR2 signaling in LY6Chi monocytes in the bone marrow.²⁹

LMR has also been demonstrated as a new systemic inflammatory indicator in many diseases, including various active infections, solid organ malignancies, hematological malignancies, and rheumatic diseases.^{9,10,12,30} As a result, the diagnostic value of this parameter may be considered doubtful or obscure. Such parameters are unlikely to be useful as definitive diagnostic criteria for certain diseases. However, nosocomial influenza is an ideal disease entity for an effective diagnostic parameter for the following reasons: First, PCR tests are expensive and have a long turnaround time. Second, influenza has a high transmission capacity, and timely diagnosis is required for implementing effective infection control measures. Third, influenza can be treated and prevented by oseltamivir, but treatment should be implemented within 48 h of onset, which again calls for a fast diagnosis. Our study has proven that parameters including LMR and NLR can be useful, timely, and cost-efficient diagnostic tools during hospital outbreaks of influenza, especially when leading cases are already confirmed by PCR or antigen testing.

Our study has several limitations. First, it was a retrospective study conducted in a single center, and the sample size was relatively small. Second, it was difficult to identify another clearly defined nosocomial outbreak as a control group. Instead, we used COVID-19 patients diagnosed in our center based on the similar presentation of the two diseases; COVID-19 patients were derived from the community rather than a hospital. Third, although ≥ 48 h after admission is the criterion for hospital infection, it is possible that they were acquired in the community. Fourth, appropriate and timely discovery of a nosocomial influenza outbreak can be challenging, especially among those with atypical influenza-like symptoms; consequently, application of our study can be limited. Therefore, further controlled studies comprising a greater number of patients from different centers are needed to validate the clinical value of lymphocytes, LMR, NLR, and PLR, and extend their generalizability and applicability for influenza diagnosis.

Conclusions

Biomarkers such as LMR and NLR are good indicators for the diagnosis of nosocomial influenza outbreaks. LMR is of particular value during the COVID-19 pandemic when simultaneous transmission of both diseases can be a substantial threat.

Abbreviations

CBC

complete blood count; LMR:Lymphocyte-monocyte ratio;

NLR

neutrophil-lymphocyte ratio; LPR:lymphocyte-to-platelet ratio;

AUC

area under the curve; ROC:receiver operating characteristic;

COVID- 19

Coronavirus disease 2019; SARS-CoV-2:Severe acute respiratory syndrome coronavirus 2; PCR:polymerase chain reaction;

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Peking Union Medical College Hospital (approval number SK301), and the requirement for informed consent was waived.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due individual privacy could be compromised but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WJL conceived this study and organized the author team. CWZ had full access to all of the data in the study and takes responsibility for the integrity and accuracy of the data. XM, WL and SFY participated in data review and statistical analysis. FJP, KFH. and TXL drafted the manuscript. All authors have read and approved the final manuscript.

FJP and KFH contributed equally to this work.

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Figures

Figure 1

Timeline of LMR, NLR and LPR in influenza patients.

Figure 2

2-1. ROC curve was used to evaluate the diagnostic value for influenza. 2-2. ROC curve was obtained by comparing Symptom Onset group with Recovery group.

Figure 3

3-1, 3-2. ROC curve was used to evaluate the diagnostic value between influenza and COVID-19.