Received: March 31, 2021

Revised: April 20, 2021

Accepted: April 20, 2021

Corresponding Author:

Sang Hun Lee, M.D.

Department of Emergency Medicine,
Keimyung University School of Medicine,
1095, Dalgubeol-daero Dalseo-gu, Daegu
42601, Korea

Tel: +82-53-258-7895

E-mail: sanghun@dsmc.or.kr

Clinically Significant Monocyte Biomarker for Differential Diagnosis of COVID-19 Pneumonia in the Emergency Department

Hyo-Won Kim¹, Jae Cheon Jeon¹, Woo Ik Choi¹, Ji Yeon Lee²,
Yong Sik Kwon³, Mi Jin Lee⁴, Jae Wan Cho⁴, Gyunmoo Kim⁵,
You Ho Mun⁶, Sang-Hun Lee¹

¹Department of Emergency Medicine, Keimyung University School of Medicine, Daegu, Korea

²Department of Infectious diseases, Keimyung University School of Medicine, Daegu, Korea

³Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea

⁴Department of Emergency Medicine, Kyungpook National University School of Medicine, Daegu, Korea

⁵Department of Emergency Medicine, Daegu Catholic University School of Medicine, Daegu, Korea

⁶Department of Emergency Medicine, Yeungnam University College of Medicine, Daegu, Korea

To determine basic patient characteristics and biomarkers to help in the early diagnosis of Coronavirus disease 2019 (COVID-19) pneumonia in patients with pneumonia who visited the emergency department (ED). This retrospective study evaluated patients diagnosed with community-acquired pneumonia (CAP) or COVID-19 pneumonia in the ED at four tertiary medical centers between February 1 and March 31, 2020. Parameters related to the differential diagnosis between CAP and COVID-19 were investigated. Clinical characteristics and laboratory results of biomarkers were analyzed. In total, 81 patients presented to the ED with COVID-19 pneumonia. Multivariate logistic regression analysis showed that monocyte count [odds ratio (OR): 0.996; 95% confidence interval (CI): 0.994–0.999] and pneumonia severity index (PSI) [OR: 1.025; 95% CI: 1.002–1.049] were associated with diagnosis of COVID-19 pneumonia. The area under the curve comprising the combination of monocyte and PSI was 0.789. Differential diagnosis of COVID-19 pneumonia from pneumonia patients who visited the ED can be made by monocyte count and PSI score.

Keywords: COVID-19, Emergencies, Monocytes, Pneumonia

Introduction

In December 2019, novel coronavirus disease 2019 (COVID-19) was first diagnosed in Wuhan, China. Subsequently, it spread worldwide and the World Health Organization declared a pandemic on March 11, 2020 [1,2]. In total, 19% of patients with COVID-19 require hospitalization, 5% require critical care, and the observed mortality rate is 2.3% [3]. In particular, the mortality rate is very high in elderly people over 80 years of age, with a rate of 14.9% [3].

The standard diagnosis of COVID-19 has a low positive rate and involves reverse-transcription polymerase chain reaction (RT-PCR) of samples collected using oropharynx swabs [4]. The testing of throat swabs or sputum increases the sensitivity, but remains insufficient for the diagnosis of all patients [5]. Recently, it has been suggested that computed tomography (CT) can aid in diagnosis through typical COVID-19 CT findings such as lung global ground-glass pat-

terns and consolidative pulmonary opacities [6]. However, Reporting RT-PCR results can take anywhere from a few hours to about 2-8 days, and CT imaging without coronavirus screening test is very limited owing to the potential exposure of the CT rooms to the virus [7]. Moreover, these tests cannot be performed in all clinics, and testing is possible only in some hospitals equipped with appropriate equipment.

In this study, we aimed to elucidate the simple biomarkers and basic characteristics that can aid the diagnosis of COVID-19 in pneumonia patients visiting the emergency room.

Material and methods

Study design and search strategy

In this retrospective study, all adult patients (aged ≥ 18 years) diagnosed with COVID-19 pneumonia or community-acquired pneumonia (CAP) and managed in emergency rooms at four tertiary medical centers in Daegu, South Korea from February 1 to March 31, 2020, were included. The study protocol was approved by the Institutional Review Board and exempted from prior consent requirements due to the retrospective nature of the study. Patients transferred from other hospitals after initial management; those who had not undergone the laboratory test; those who had other infection, and those who had other kinds of diseases, such as coronary artery disease, heart failure, renal failure, liver disease, malignancy, rheumatic disease, stroke, pulmonary disease, or hemato-oncology disease, were excluded.

Enrolled CAP patients were those showing abnormal lung parenchyma such as a new patchy infiltrate, leaf or segment consolidation, ground-glass opacity, or interstitial change on chest radiograph, due to respiratory infections acquired outside the hospital [8]. This diagnosis was done by an emergency medicine or internal medicine specialist. COVID-19 pneumonia was diagnosed based on RT-PCR results of nasopharynx swab or sputum and image of X-ray or CT findings. It was not included if only swab was positive or only image was positive. Chest CT findings used to diagnose COVID-19 pneumonia included pure ground-glass opacities (GGOs), GGOs with interstitial and/or interlobular septal thickening, and GGOs with consolidation [9]. All CT results were reported by board-certified radiologists on duty.

Other data, including age, sex, comorbid disease, vital signs, mental status, laboratory data, pneumonia severity index (PSI), CURB-65, length of stay in the hospital, and 28-day mortality, were retrieved from all patients' electronic medical records. The biomarkers comprising neutrophil-to-lympho-

cyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) were calculated.

Statistical analysis

Continuous variables were reported as mean $\pm$ standard deviation or median and inter-quartile range, with parametric data compared using Student's t-tests and non-parametric using the Mann-Whitney U test. Categorical variables were reported as number (percentage) and compared using the χ^2 test with Yates correction or the Fisher's exact test, as warranted. Variables with statistical significance were tested by binary logistic regression analysis, and its odds ratio (OR) and 95% confidence interval (CI) were calculated. The area under curve (AUC) value, optimal cutoff value, sensitivity, and specificity were determined using receiver operating characteristic (ROC) curve. All statistical analyses were performed using SPSS 21 (SPSS Inc., Armonk, NY, United States), with a two-sided p -value < 0.05 considered statistically significant.

Results

During the study period, 226 patients visited the A medical center emergency department exhibiting pneumonia. After excluding 169 patients due to predetermined criteria, 57 patients were enrolled, including 40 CAP patients and 17 COVID-19 pneumonia patients. Sixty-four patients with COVID-19 pneumonia were enrolled from three other university hospitals in Daegu (Fig. 1).

In total, 81 COVID-19 pneumonia patients, including 38 (46.9%) men and 43 (53.1%) women, of mean age 65.8 years (range 25-95 years) were analyzed. On comparison of CAP and COVID-19 groups, the COVID-19 group depicted a decrease in absolute monocyte count (580/ μ L vs. 380/ μ L, $p < 0.001$), absolute neutrophil count (6,200/ μ L vs. 5,600/ μ L, $p = 0.031$), MLR (0.52 vs. 0.38, $p = 0.05$), erythrocyte sedimentation rate (67 mm/h vs. 53 mm/h, $p = 0.040$), and albumin (4.0 g/dL vs. 3.5 g/dL, $p < 0.001$), while prothrombin time (1.03 vs. 1.11, $p < 0.001$), D-dimer (0.68 μ g/mL vs. 1.21 μ g/mL, $p = 0.023$), CK-MB (0.96 μ g/mL vs. 1.40 μ g/mL, $p = 0.008$), lactic acid (1.1 mmol/L vs. 1.6 mmol/L, $p = 0.001$), and PLR (178.97 vs. 235.78, $p = 0.002$) increased. Severity indexes, including CURB-65, PSI, and 28-day mortality were higher in the COVID-19 pneumonia group (Table 1).

A comparison of the AUC between the monocyte count and MLR area score revealed that the area of monocyte count was higher (AUC [95% CI]: 0.697 [0.590 to 0.803] and 0.658 [0.556 to 0.761], respectively). The PSI area score was found

Fig. 1. Flowchart of the study patients.

to be higher on comparing the CURB-65 and PSI area scores by the AUC of the ROC curve. (AUC [95% CI]: 0.550 [0.439 to 0.661] and 0.637 [0.524 to 0.750], respectively) (Table 2, Fig. 2).

All the factors showing significance were further analyzed by multivariate analysis. Lower monocyte count (OR: 0.996; 95% CI: 0.994-0.999, $p = 0.002$), and higher PSI (OR: 1.025; 95% CI: 1.002-1.049, $p = 0.035$), were factors significantly associated with diagnosis of the COVID-19 pneumonia (Table 3). The AUC representing combination of monocyte and PSI was 0.789. (95% CI: 0.700-0.878, $p < 0.001$) (Fig. 3).

Discussion

Differentiation of COVID-19 pneumonia from CAP could have important treatment implications. Although RT-PCR is used to detect COVID-19 virus, it has imperfection and is time consuming [5,7]. As a result, the use of other variables is necessary to distinguish between CAP and COVID-19 pneumonia. To our knowledge, this is the first study to investigate the biomarkers associated with COVID-19 pneumonia. In this study, we attempted to clarify the difference between CAP and COVID-19 pneumonia through an initial biomarker result and the patient's character when the emergency room was visited. COVID-19 pneumonia was shown to be significantly predicted by monocytes, a biomarker, as well as PSI, which is a measure of pneumonia severity.

Although technological advances for the diagnosis of viral pneumonia are ongoing, they are still insufficient to clarify

the cause of pneumonia [10]. In particular, the upper respiratory tract infection is detected using nasopharyngeal swabs, which are easy to collect, but lower respiratory specimens obtained via sputum are not only difficult to obtain, but also pose difficulty in distinguishing infection from colonization or long-term shedding [11]. Therefore, the variables such as individual basic characters and clinical profiles, biomarkers, imaging results, and treatment response prove to be useful in distinguishing viral pneumonia from bacterial pneumonia [12]. White blood cell (WBC), C-reactive protein (CRP), and procalcitonin (PCT) showed comparatively high values in bacterial pneumonia and use of antibiotics in an early stage, helped improve patient prognosis [8,12]. Blood test parameters for the diagnosis of CAP revealed that NLR and MLR were significant, and it was found that monocyte had a diagnostic value in patients with liver injury [13]. The value of a biomarker is affected by multiple underlying diseases including tumors, infectious diseases, renal failure, rheumatic diseases cardiovascular disease, etc. [14-16]. Therefore, this study excluded patients with underlying illnesses, except hypertension and diabetes. The results of this study showed that CRP and PCT did not differ between CAP and COVID-19 pneumonia, but WBCs were significantly different and lower in count in COVID-19 pneumonia patients. (7,880/ μ L vs. 7,020, $p = 0.025$) The neutrophil and monocyte count of the WBC showed a statistically significantly lower value in the COVID-19 pneumonia group, and only MLR showed a statistically significant lower value when calculated via the ratio with lymphocytes. The AUC of the difference between COVID-19 pneumonia and CAP for

Table 1. Demographic and clinical characteristics of the community-acquired pneumonia and COVID-19 pneumonia

	CAP (n = 40)	COVID-19 (n = 81)	p-Value
Age (years)	59.2 (24-92)	65.8(25-95)	0.083
Sex, male (%)	21 (52.5)	38 (46.9)	0.350
Previous illness			
Hypertension (%)	13 (32.5)	34 (42)	0.210
Diabetes (%)	7 (17.5)	17 (21)	0.423
Vital sign			
Systolic blood pressure (mmHg)	130 (115-150)	130 (117-150)	0.493
Diastolic blood pressure (mmHg)	80 (70-90)	80 (70-90)	0.235
Pulse rate (heart rate/minute)	97 (81.3-113.8)	87 (78-104)	0.060
Body temperature (°C)	37.7 (36.9-38.5)	37.2 (36.6-38.0)	0.014
O2 saturation (%)	96.0 (92.5-97.0)	96.0 (90.0-99.0)	0.318
Laboratory finding			
White blood cell (× 1,000/μL)	7.88 (5.60-14.28)	7.02 (5.01-9.06)	0.025
Absolute neutrophil count (x 1,000/μL)	6.22 (4.54-11.91)	5.60 (3.30-7.83)	0.031
Absolute lymphocyte count (x1,000/μL)	1.02 (0.73-1.33)	0.91 (0.69-1.21)	0.117
Absolute monocyte count (x1,000/μL)	0.58 (0.37-0.87)	0.38 (0.25-0.54)	< 0.001
Platelet (x1,000/μL)	208 (163-275)	222 (154-297)	0.314
C-reactive protein (mg/dL)	5.4 (1.9-11.7)	7.9 (2.5-15.1)	0.217
ESR (mm/h)	67 (40-85)	53 (36-71)	0.040
Procalcitonin (ng/mL)	0.139 (0.057-0.416)	0.131 (0.059-0.318)	0.340
Hemoglobin (g/dL)	12.9 (12.0-14.4)	13.1 (12.1-14.2)	0.449
Prothrombin time (INR)	1.03 (0.98-1.10)	1.11 (1.06-1.22)	< 0.001
Cr (mg/dL)	0.92 (0.75-1.24)	0.83 (0.7-1.1)	0.196
Albumin (g/dL)	4.0 (3.6-4.4)	3.5 (3.3-3.9)	< 0.001
Total bilirubin (mg/dL)	0.5 (0.4-0.6)	0.6 (0.4-1.0)	0.083
D-dimer (μg/mL)	0.68 (0.41-1.61)	1.21 (0.60-2.77)	0.023
CK-MB (μg/mL)	0.96 (0.65-2.27)	1.40 (1.00-2.70)	0.008
BNP (pg/mL)	147 (94-581)	216 (122-511)	0.186
pH	7.433 (7.377-7.464)	7.444 (7.409-7.470)	0.164
Lactic acid (mmol/L)	1.1 (0.8-1.6)	1.6 (1.2-2.3)	0.001
NLR	6.47 (4.21-12.54)	6.10 (3.15-10.57)	0.195
PLR	178.97 (144.9-298.23)	235.78 (164.86-338.49)	0.002
MLR	0.52 (0.36-0.86)	0.38 (0.28-0.55)	0.050
CURB-65	1 (0-2)	1 (0-2)	0.023
PSI	66 (42-94)	82 (65-98)	0.005
28-day mortality	2 (5)	15 (12.4)	0.032

ESR, erythrocyte sedimentation rate; Cr, creatinine; BNP, brain natriuretic peptide; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; MLR, monocyte lymphocyte ratio; CURB-65 (confusion, blood urea > 42,8 mg/dL, respiratory rate > 30/min, blood pressure < 90/60 mmHg, age > 65 years); PSI, pneumonia severity index.

Table 2. Diagnostic value of predictive factors for COVID-19 pneumonia

	AUC	CI 95%	p-Value	Optimal cutoff value	Specificity	Sensitivity
Monocyte	0.697	0.590-0.803	< 0.001	456.78	64.2	65
MLR	0.658	0.556-0.761	0.005	0.48	66.7	60
CURB-65	0.550	0.439-0.661	0.372	0.5	42.5	57.5
PSI	0.637	0.524-0.750	0.014	74	62.5	63
Monocyte and PSI	0.789	0.700-0.878	< 0.001		67.5	76.5

MLR, monocyte lymphocyte ratio; CURB-65 score (confusion, blood urea > 42,8 mg/dL, respiratory rate > 30/min, blood pressure < 90/60 mmHg, age > 65 years); PSI, pneumonia severity index.

Fig. 2. (A) Receiver operating characteristic curve in monocyte and monocyte/lymphocyte ratio. (B) Receiver operating characteristic curve in pneumonia severity index and CURB-65.

Table 3. Multivariate logistic regression analysis of factors affecting COVID-19 pneumonia diagnosis

	Odds Ratio	95% confidence interval	p-Value
Monocyte	0.996	0.994-0.999	0.002
PSI	1.025	1.002-1.049	0.035

PSI, pneumonia severity index.

Fig. 3. Receiver operating characteristic curve in integrated factor.

monocyte and MLR was 0.697 and 0.658 respectively, and monocyte showed higher value.

COVID-19 pneumonia is more severe than other pneumonia. Therefore, a score indicating the severity of pneumonia can be helpful in clinical judgment [3]. The most commonly used scores are PSI and CURB-65 [17,18]. The PSI had divided patients into five severity classes, composed of 20 items associated with mortality risk.[17] CURB-65 is more convenient than the PSI for assessing the severity of pneumonia using only 5 items, excluding comorbidities [18]. From the results of this study, the severity of COVID-19 pneumonia was higher in PSI (66 vs. 82, $p = 0.005$) and 28-day mortality (5% vs. 12.4%, $p = 12.4\%$). AUC of the PSI ROC was 0.637 and the cut-off value was observed at 74. CURB-65 score consisted of only 5 points, could not subdivide patient severity, and was equally observed with a median value of 1 in both COVID-19 pneumonia and CAP groups.

This study had some limitations. Firstly, this study was a retrospective study and included relatively small sample size and selective exclusion of the previous disease. Considering this retrospective nature of the study, caution is required when interpreting and applying the current results, because not all patients are able to provide precise information. Secondly, the subsequent period was relatively short; hence we could not identify the long-term outcomes. Therefore, additional controlled studies involving a larger number of patients are need-

ed to validate the clinical value of monocytes in COVID-19 pneumonia. Thirdly, CAP patients were collected only in one hospital and were fewer than COVID-19 patients. Therefore, additional controlled studies involving a larger number of patients included various underlying disease are needed to validate the clinical value of monocytes in COVID-19 pneumonia.

In conclusion, this study is the first report on the relationship between monocyte and diagnosis of COVID-19 pneumonia. We believe that the combination of a wide and readily available monocyte and PSI score could be helpful in the diagnosis of COVID-19 pneumonia.

Conflict of interest

All authors declare no conflicts-of-interest related to this article.

Acknowledgements

This study was supported by a research grant from Daegu Medical Association COVID-19 scientific committee.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382:727-33.
2. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19). [cited 2020 Apr 5]. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/summary.html>.
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239-42.
4. Zhang W, Du RH, Li B, Zheng XS, Yang XL, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect*. 2020;9:386-9.
5. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. *Radiology*. 2020;296:E115-7.
6. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology*. 2020;295:202-7.
7. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. *Int J Antimicrob Agents*. 2020;55. DOI: 10.1016/j.ijantimicag.2020.105955.
8. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet*. 2015;386:1097-108.
9. Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology*. 2020;295:210-7.
10. Murdoch DR, O'Brien KL, Scott JA, Karron RA, Bhat N, Driscoll AJ, et al. Breathing new life into pneumonia diagnostics. *J Clin Microbiol*. 2009;47:3405-8.
11. Murdoch DR, Jennings LC, Bhat N, Anderson TP. Emerging advances in rapid diagnostics of respiratory infections. *Infect Dis Clin North Am*. 2010;24:791-807.
12. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. *Lancet*. 2011;377:1264-75.
13. Huang Y, Liu A, Liang L, Jiang J, Luo H, Deng W, et al. Diagnostic value of blood parameters for community-acquired pneumonia. *Int Immunopharmacol*. 2018;64:10-5.
14. Wang JL, Lu XY, Xu XH, Zhang KJ, Gong H, Lv D, et al. Predictive role of monocyte-to-lymphocyte ratio in patients with Klebsiella pneumonia infection: a single-center experience. *Medicine (Baltimore)* 2019;98. DOI: 10.1097/md.00000000000017215.
15. Ji H, Li Y, Fan Z, Zuo B, Jian X, Li L, et al. Monocyte/lymphocyte ratio predicts the severity of coronary artery disease: a syntax score assessment. *BMC Cardiovasc Disord*. 2017;17:90.
16. Feng F, Sun L, Zheng G, Liu S, Liu Z, Xu G, et al. Low lymphocyte-to-white blood cell ratio and high monocyte-to-white blood cell ratio predict poor prognosis in gastric cancer. *Oncotarget*. 2017;8:5281-91.
17. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243-50.
18. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377-82.