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임상화학

코로나바이러스감염증-19 (COVID-19) 환자의 폐 손상 예측 인자로서 C-반응단백질 검사의 활용

Utilization of C-Reactive Protein Test as a Predictor of Lung Injury in Patients with Coronavirus Disease 2019

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Background: C-reactive protein (CRP) test can be used at coronavirus disease 2019 (COVID-19) screening clinics as a point of care test. The aim of this study was to determine whether CRP test can be used as an indicator of lung injury.
Methods: In all, 98 patients with COVID-19 were enrolled for this study. We collected medical records and laboratory results of the patients. Chest radiographic findings were classified into five groups. We analyzed the correlation between laboratory tests and the grade of lung injury.
Results: In patients with COVID-19, increased CRP and erythrocyte sedimentation rate (ESR), and lymphocytopenia were noted. CRP, ESR, and segmented neutrophils were found to be positively correlated while albumin and lymphocyte were negatively correlated with lung injury grade. CRP levels showed the highest correlation coefficient of 0.858. Based on the chest radiographs, the sensitivity and specificity of CRP was 100% and 77.8%, respectively. Within the reference range of CRP, abnormal chest radiograph was not recognized. In addition, initial and subsequent increase in CRP levels in patients with unremarkable chest radiograph could be associated with aggravated lung injury.
Conclusions: CRP test showed a sensitivity of 100% in detection of lung injury, and the level was proportional to the extent of lung lesions. Therefore, CRP test will be useful as a predictor of lung injury in patients with COVID-19.

Key Words: Coronavirus disease 2019, C-reactive protein, Lung injury

INTRODUCTION

On March 11, 2020, WHO characterized the new coronavirus outbreak as a pandemic. Coronavirus disease 2019 (COVID-19) has spread in more than 213 countries worldwide, and the total number of the patients has exceeded 10,000,000 as of July 2, 2020 (https://covid19.who.int/).

The largest number of COVID-19 patients in South Korea (N=6,833) was recorded in Daegu, where the spread of the disease was caused by a specific religious group called Sincheonji (https://coronaboard.kr/). The Daegu Catholic University Medical Center (DCUMC) had 98 confirmed COVID-19 patients as of March 10, 2020.

The lung is the main target organ of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1, 2]; therefore, it is essential to perform radiographical examination for lung injury. To detect lung injury, chest computed tomography (CT) is more accurate than chest radiograph, but chest CT is not available for screening of large number of people. Though the chest radiograph could be utilized for mass screening, it is difficult to obtain

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in a short time in an emergency clinic.

In this study, we compared the C-reactive protein (CRP) test levels with chest radiograph findings. Many patients visit COVID-19 screening clinics, but many are required to wait in their own home due to lack of hospitalization. To determine admission, doctors refer to patient's temperature and clinical symptoms, but they are not an objective criterion. CRP test can be used at screening clinics as a point of care test [3]. If CRP test is correlated with the chest radiograph findings, it can be used as a criterion for determining admission of patients with COVID-19. Some studies have identified objective markers for assessing the severity of disease in COVID-19 patients [4-8]. In previously reported meta-analyses [9, 10], CRP, albumin, erythrocyte sedimentation rate (ESR), eosinopenia, interleukin-6, and neutrophil-to-lymphocyte ratio were the most prevalent laboratory findings. Among those markers, CRP was most frequently described [4-6]. Studies on CRP levels and extent of lung injury were conducted by several researchers [4, 8, 11], but the number of cases in their studies were small (12 to 27 cases) and they did not focus on the clinical usefulness of CRP. Here, we intended to clarify the clinical significance of CRP through detailed analysis and follow-up of CRP levels and lung injury.

MATERIALS AND METHODS

In all, 98 patients were enrolled for this study, from which, 79 patients were diagnosed at other hospitals and were transferred to the DCUMC (Daegu, Korea). The remaining 19 patients were diagnosed and admitted at the DCUMC. Reverse-transcription polymerase chain reaction (RT-PCR) for COVID-19 was conducted using upper and/or lower respiratory specimens at DCUMC using Powerchek™ 2019-nCoV Real-time PCR kit (Kogene Biotech, Seoul, Korea). PCR was performed with a CFX96 real-time PCR detection system (Bio-Rad, Hercules, CA, USA). We collected medical records of the patients from February to March 2020 using electric medical records of DCUMC. The chest radiograph findings were read by two radiologists. They classified the chest radiographic findings into five groups according to arbitrary criteria based on the extent of infiltration as follows: unremarkable finding (grade 0), less than 25% of total lung volume (grade 1), 25 to 50% of total lung volume (grade 2), 50 to 75% of total lung volume (grade 3), and greater than 75% of total lung volume (grade 4) (Table 1 and Fig. 1). As only one case belonged to grade 4, it was reclassified as grade 3 for statistical analysis. We used the UniCel DxH 800 (Beckman Coulter, Brea, CA, USA) for hematology tests, cobas c 702 (Roche Diagnostics, Rotkreuz, Switzerland) for biochemical tests, and Test1 (AliFax, Padova, Italy) for ESR tests. This study was approved by the Institutional Review Board (IRB) of DCUMC (CR-20-051-PRO-001-R).

Statistical analysis was performed using IBM SPSS 19.0. Spearman rank correlation analysis was used for determining the association between laboratory results and lung injury grade. Kruskal Wallis test was used for determining the significance of CRP lev-

Table 1. Demographic and clinical characteristics of and correlation with lung injury grade in patients with COVID-19 (N=98)

Characteristics	Data	Correlation coefficient
Age (yr)	56.8 ± 18.9	
M:F ratio	0.53:1	
Clinical symptoms		
Fever	42 (42.9)	NA
Chill	25 (25.5)	NA
Cough	58 (59.2)	NA
Sputum	44 (44.9)	NA
Sore throat	18 (18.4)	NA
Dyspnea	41 (41.8)	NA
Cheat pain	12 (12.2)	NA
Headache	29 (29.6)	NA
Laboratory results (Reference range)		
CRP (≤ 5 mg/L)	25.0 ± 32.4	0.858*
Albumin (3.5–5.1 g/dL)	3.9 ± 4.4	-0.631*
Glucose (74–100 mg/dL)	119.8 ± 57.2	0.448*
ALT (< 40 U/L)	28.2 ± 27.7	0.325*
eGFR (> 90 mL/min/1.7 m^2)†	90.2 ± 24.5	-0.366*
Hemoglobin (M12.9–16.9, F10.7–14.6 g/dL)	128 ± 18.0	-0.130
WBC (3.6–9.6×10^9/L)	5.52 ± 2.67	0.245
Segmented WBC (×10^9/L)	3.58 ± 2.52	0.456*
Lymphocyte (×10^9/L)	1.33 ± 0.56	-0.572*
Monocyte (×10^9/L)	0.50 ± 0.27	0.060
ESR (M ≤ 10, F ≤ 20 mm/hr)	45.5 ± 30.8	0.796*
Chest radiograph grades‡		
Grade 0 (No)	54 (55.1)	NA
Grade 1 (< 25%)	15 (15.3)	NA
Grade 2 (25–50%)	15 (15.3)	NA
Grade 3 (50–75%)	13 (13.3)	NA
Grade 4 (> 75%)	1 (1.0)	NA

Data are number (%) or means ± standard deviation.
*Statistically significant with $P < 0.05$ based on Spearman rank correlation analysis; †Creatinine eGFR (CKD-EPI equation 2009); ‡Percentage of lung infiltration/total lung volume.
Abbreviations: ALT, alanine aminotransferase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; F, female; M, male; WBC, white blood cell; NA, not applicable.

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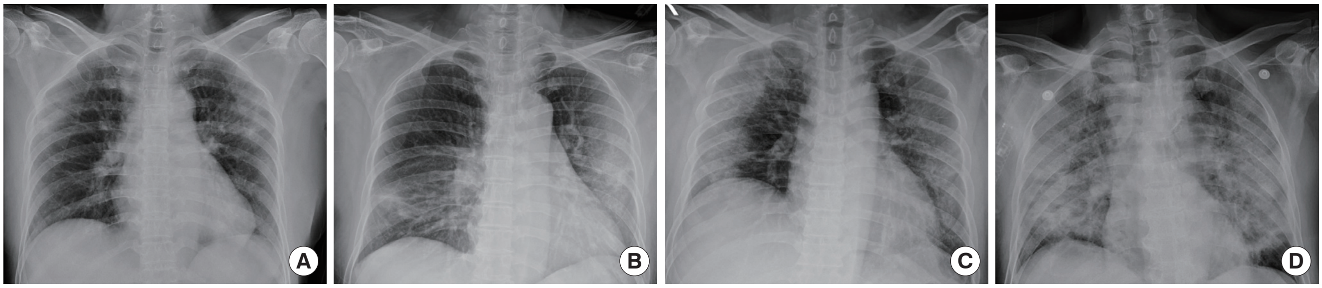

Fig. 1. (A) Patchy consolidations in both upper lung fields (Grade 1). The lesion was improved, and the patient was discharged without sequelae 17 days later (CRP: 19.5 mg/L). (B) Patchy consolidations in the right lower lung and left middle and lower lung fields (Grade 2). The lesion was improved, and the patient was discharged without sequelae 1 month later (CRP: 44.7 mg/L). (C) Peripherally located consolidations in both lung fields (Grade 3). The patient was discharged without sequelae 1 month later (CRP: 120 mg/L). (D) Diffuse consolidations in both lung fields (Grade 4). The patient died of acute respiratory distress syndrome 10 days later despite aggressive antiviral therapy (CRP: 79.5 mg/L).

els according to the lung injury grade. Repeated measurement ANOVA was performed to compare the difference in serial CRP values between patients with unchanged (grade 0) and aggravated (grade 1-4) chest radiographic findings monitored for 14 days.

RESULTS

1. Demographic and clinical characteristics

The average age and M:F ratio among the 98 patients were 56.8 ±18.9 years and 0.53:1, respectively. The average number of days between COVID-19 diagnosis and initial blood sample collection following hospitalization was 4.3±1.9 days. Cough appeared most frequently (59.2%), followed by sputum (44.9%), fever (42.9%), and dyspnea (41.8%). In the laboratory results, increased CRP and ESR, and lymphocytopenia were noted. Fifty-four patients (55.1%) showed no active pulmonary lesions on chest radiograph (Table 1). Fig. 1 provides typical chest radiographs by the lung injury grade. There was no evidence of bacterial superinfection in any patient.

2. Correlation of chest radiographic findings with laboratory tests

We calculated correlation coefficients between chest radiograph findings and laboratory tests (Table 1). The blood collection and laboratory tests were performed within 0-1 day of chest imaging for all patients. CRP, ESR and segmented neutrophils showed a positive correlation while albumin and lymphocyte showed a negative correlation with lung injury grade. The results revealed that CRP levels had the highest correlation coefficient of 0.858.

Table 2. Diagnostic values of CRP test for lung injury according to CRP level

CRP (mg/L)	Chest PA	
	Abnormal*	Unremarkable
>5 (N=56)	44	12
≤5 (N=42)	0	42
Total (N=98)	44 Sensitivity 100% PPV 78.6%	54 Specificity 77.8% NPV 100%

CRP (mg/L)	Abnormal rates of chest PA in the increased CRP group
	Abnormal chest PA
5-20 (N=19)	9 (47.4%)
20-50 (N=19)	17 (89.5%)
>50 (N=18)	18 (100%)

*Abnormal chest radiograph from grade 1 to grade 4.
Abbreviations: CRP, C-reactive protein; NPV, negative predictive value; PA, posteroanterior; PPV, positive predictive value.

3. CRP and chest radiograph

Based on the chest radiographs, CRP test showed 100% sensitivity and 77.8% specificity (Table 2). In the group with normal CRP (≤5 mg/L), all chest radiographs were unremarkable, and in the group with increased CRP (>5 mg/L), abnormalities were observed in 78.6% of chest radiographs. In groups with CRP in the range of 5 to 20 and 20 to 50 mg/dL, abnormalities were observed in 47.4% and 89.5% of chest radiographs, respectively, while in the group with over 50 mg/dL CRP, all patients had abnormal chest radiograph (Table 2). The distribution of CRP concentration by the lung injury grade is shown in Fig. 2. CRP levels were significantly different according to the lung injury grade. In each group of injury grade, CRP showed high odds ratio and odds ratio increased in proportion to the CRP level (Table 3).

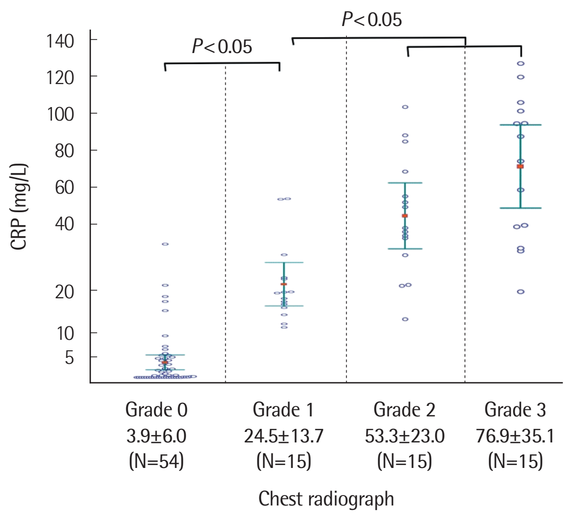

Fig. 2. Distribution of CRP levels according to the lung injury grade. Kruskal Wallis test was used for determining the significance of CRP levels according to the lung injury grade.

Table 3. Multinomial logistic regression for CRP according to the chest injury grade

Chest injury grade (Reference: Grade 0)	CRP (mg/L)	OR	95% Confidence Interval for OR	*P*-value
Grade 1	<5	1	-	-
	5-20	58.8	3.075-1124.407	0.007*
	20-50	252	10.120-6275.150	0.001*
	>50	336	5.198-21717.724	0.006*
Grade 2	<5	1	-	-
	5-20	8.4	0.263-268.378	0.229
	20-50	294	11.976-7217.373	0.001*
	>50	1,176	21.521-64260.947	0.001*
Grade 3	<5	1	-	-
	5-20	8.4	0.263-268.378	0.229
	20-50	168	6.421-4395.324	0.002*
	>50	1,512	28.096-81369.142	0.000*

*Statistically significant with $P<0.05$.
Abbreviations: CRP, C-reactive protein; OR, Odds ratio.

4. Follow up of CRP test and chest radiograph

We analyzed serial CRP values on days 1, 4, 7, 10, and 14 in the 54 patients with unremarkable chest radiograph on admission (grade 0). Forty-three patients had no change in chest radiograph and 11 had aggravated chest findings for 14 days. The serial CRP values between the unchanged and aggravated groups were significantly different ($P<0.001$, Fig. 3). Among 12 patients who showed increased CRP concentration with unremarkable chest radiograph, 11 patients had abnormal chest radiograph or chest CT findings after 4 to 12 days (Table 4).

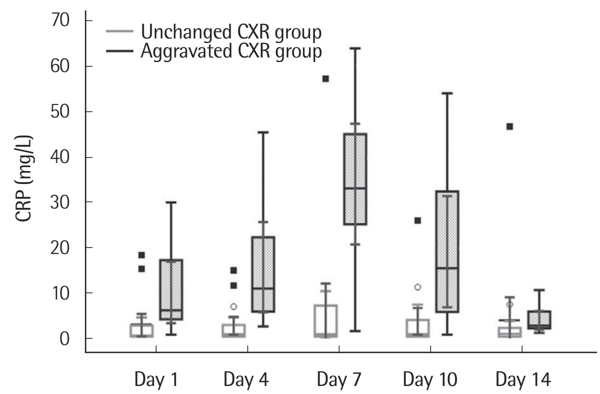

Fig. 3. Comparison of the serial CRP values between patients with unchanged (grade 0) and aggravated (grade 1-4) chest radiographic (CXR) findings monitored for 14 days.

DISCUSSION

In this study, increased CRP and ESR, and lymphopenia were noted in COVID-19 patients. CRP, ESR and segmented neutrophils showed a positive correlation while albumin and lymphocyte showed a negative correlation with lung injury grade. CRP test showed the highest correlation (r=0.858), 100% sensitivity, and 77.8% specificity compared to the chest radiograph findings. Abnormal chest radiograph was not detected in the reference range of CRP. In addition, initial and subsequent increase in CRP levels in patients with unremarkable chest radiograph could be associated with aggravated lung injury. CRP is one of the strongest acute phase reactants and is increased in various infections and inflammatory diseases [12]. CRP aids in non-specific host defense against infectious organisms by activating the classical complement pathway [13]. Concentration of CRP is generally higher in bacterial infection than in viral infection [14]. CRP levels increase within 6 to 12 hours after the onset of inflammation or injury and peak at about 48 hours and they are generally proportional to the extent of tissue damage [12].

Zhao et al. [15] found that angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV-2. In the human lung, ACE2 is expressed on type I and II alveolar epithelial cells. Among them, 83% of the type II alveolar cells have express ACE2 [15]. The binding of SARS-CoV-2 on ACE2 causes an elevated expression of ACE2, which can lead to damage to alveolar cells. Damage to alveolar cells can trigger a series of systemic reactions and even death. About a third of patients presented with acute respiratory distress syndrome, showing desquamation of pneumocytes and

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Table 4. Follow-up test results for 12 patients with increased CRP (mg/L) and normal chest radiographic findings on admission

Cases	Sex	Age (yr)	CRP-1st	Interval (day)	CRP-2nd	Chest PA-2nd / Chest CT
Case 1	M	24	5.1	10	0.6	NAPL
Case 2	M	79	5.5	12	32.5	NAPL/Multiple GGO-both lung
Case 3	F	78	5.5	7	13.7	Increased opacity/focal GGO-LLL
Case 4	F	56	5.9	8	60.4	Patchy consolidation-RML
Case 5	F	77	6.8	8	35.6	Patchy consolidation-RLL
Case 6	F	56	7.5	5	6.1	Patchy consolidation-Left CP angle
Case 7	M	52	9.8	11	0.9	NAPL/Multiple GGO-RLL
Case 8	F	58	15.4	7	10.6	NAPL/Multiple GGO-LLL
Case 9	M	28	17.4	4	45.5	Patchy opacity-BLL
Case 10	M	51	18.5	5	4.8	NAPL/Multiple GGO-BLL
Case 11	F	69	21.0	8	25.3	Focal opacity-BLL
Case 12	F	70	30.1	9	56.5	Multifocal patchy opacity-both lung

Abbreviations: BLL, both lower lobes; CP, costophrenic; CRP, C-reactive protein; CT, computed tomography; F, female; GGO, ground glass opacity; LLL, left lower lobe; M, male; PA, posteroanterior; RLL, right lower lobe.

hyaline membrane formation [16, 17]. Abnormalities in chest CT images were found in nearly 100% of the patients [1, 18]. Therefore, it is important to find an objective marker that can predict the extent of lung injury.

In this study, the positive rates of initial symptoms (fever 42.9% and cough 59.2%) were not high as in other studies [1, 19]. Patient's symptoms are important in the diagnosis of COVID-19 but are difficult to use to predict lung injury. In the correlation analysis, CRP showed the highest correlation (r=0.858) with the lung injury grade followed by ESR (r=0.796). Lymphocytopenia was commonly detected [17, 20], suggesting that COVID-19 might act on lymphocytes, especially T lymphocytes [19]. The mechanism of lymphopenia includes direct infection and destruction of lymphocytes [21] and cytokine mediated lymphocyte destruction [22]. In other studies, the correlation coefficient between CRP levels and extent of lung injury was 0.59 [11], 0.62 [4], and 0.87 [8]. CRP may be the best indicator of lung injury compared to other laboratory parameters. In a study by Liu et al. [11], albumin and lymphocytes were more correlated with lung injury compared to CRP. Generally, serum albumin concentration is influenced by age (r=-0.504, this study, data not shown); hence, the direct association between albumin and lung injury will not be high. All those who showed abnormal chest radiograph had increased CRP levels. In the group of patients with normal CRP levels, none of the patients had active pulmonary lesions on the chest radiograph. As chest radiograph is less sensitive compared to chest CT, normal CRP levels cannot be used to confirm no lung injury. In the groups of patients with increased CRP levels, CRP levels were proportional to the positive rate and degree of lung injury. Compared to the other studies that analyzed the association between lung injury and CRP [4, 8, 11], this study showed the highest correlation and odds ratio. We also obtained high sensitivity and specificity with the lowest cut-off value.

Among 54 patients of grade 0, the group with aggravated chest radiographic findings showed higher initial and subsequent CRP levels than the group with unchanged chest radiographic findings. Initial and subsequent increase in CRP levels was associated with aggravated lung injury. For the 12 patients with unremarkable chest radiographs and increased CRP levels, we followed up with CRP test and chest radiograph. Except one patient (Case 1), all patients had lung injury findings while two of them (Case 7 & 10) showed normal CRP levels with multiple ground glass opacity lesion by chest CT on follow up test. This discrepancy might be explained by short half-life of CRP (4 to 7 hours) [12] and long resolution time of ground glass opacity (5 to 10 days) [18, 23]. CRP levels have been routinely used in clinical laboratories to detect or monitor inflammatory status of the patients. Though CRP is not lung specific, its application as lung injury marker would be especially useful for initial classification and follow-up of COVID-19 patients.

Limitations of this study were limited number of enrolled cases and less sensitivity of chest radiograph compared to chest CT. Though the number of patients was not high, the results of this study were statistically significant. Chest CT examination is considered superior to chest radiograph for determining the degree of lung injury, but chest CT examination is expensive and not readily available in many hospitals. In the future, we will study the correlation between chest CT findings and CRP levels.

In conclusion, CRP test showed a sensitivity of 100% in detecting lung injury, and the level was proportional to the extent of lung lesion. Therefore, CRP test will be useful as a predictor of lung injury in patients with COVID-19.

요 약

배경: C-반응단백질(C-reactive protein, CRP) 검사는 COVID-19 선별진료소에서 현장검사로도 사용할 수 있다. 이 연구에서는 CRP 검사가 COVID-19환자의 폐 손상을 예측하는 지표로 사용될 수 있는지 여부를 확인하고자 하였다.
방법: 총 98명의 COVID-19 환자의 의무기록과 검사실 및 영상의학적 검사결과를 수집하였다. 흉부 방사선 소견은 5개의 그룹으로 분류하여 검사실 검사와 폐 손상 등급 간의 상관관계를 분석하였다.
결과: COVID-19 환자에서 증가된 CRP와 ESR 및 림프구감소증이 관찰되었다. 폐 손상 등급에 따라 CRP, ESR 및 호중구 수는 양의 상관관계를 보인 반면, 알부민과 림프구 수는 음의 상관관계를 보였다. CRP가 폐 손상 정도와 가장 높은 상관계수(r=0.858)를 보였으며, 흉부 방사선 사진 결과와 비교하여 CRP 검사는 100%의 민감도와 77.8%의 특이도를 보였다. CRP가 참고 범위 내에 있는 환자에서는 비정상적인 흉부 방사선 소견은 확인되지 않았다. 초기 흉부 방사선 상 특이 소견이 없었으나 이후 비정상 소견이 나타난 환자에서 초기 및 연속적으로 측정한 CRP값이 높았다.

결 론

폐 손상에 대해 CRP 검사는 100%의 민감도를 보였으며, 폐병변의 정도에 비례하였다. 따라서, CRP 검사는 COVID-19 환자의 초기 진단 시 폐 손상을 예측하는데 유용한 지표이다.

Conflicts of Interest

None declared.

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