

Relationship between Covid-19 pneumonia intensity with lymphopenia and CRP levels

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ABSTRACT

Introduction: COVID-19 is a highly contagious and deadly disease. However, there is no accurate diagnostic test to predict its severity. The aim of this study was to determine the relationship between the lymphocyte counts and CRP levels and the severity of pulmonary involvement shown in the CT scan of the patients with pneumonia caused by COVID-19. **Methods:** In this cross-sectional study, demographic information and laboratory findings of the patients with COVID-19 were collected. Then, each patient's pulmonary involvement was scored based on the CT scan results. The data were analyzed using SPSS 16 software as well as ANOVA, chi-square test, Pearson correlation coefficient, and ROC curve. **Results:** Data of 125 COVID-19 patients with the mean age of 59.37 ± 1.5 showed that the prevalence of lymphocytes $< 1100 \times 10^9/L$ and CRP > 100 mg/L was higher in the patients with severe pulmonary involvement than in those with mild involvement ($p < 0.001$). Furthermore, an increase in pulmonary involvement severity observed in HRCT led to decreased absolute blood lymphocyte count and increased CRP levels ($p < 0.001$). The CRP test with an area under the ROC curve of 0.76 could be an acceptable test for predicting the severity of pulmonary involvement in patients with pneumonia caused by COVID-19. **Conclusion:** It was found out in this study that there was a significant positive correlation between CRP levels and the severity of COVID-19 pneumonia. The CRP test could also be an acceptable test for predicting the severity of pulmonary involvement in COVID-19.

Key words: COVID-19, Pneumonia, Lymphopenia, CRP level

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INTRODUCTION

The outbreak of COVID-19 caused by the SARS-CoV-2 virus began in December 2019 in Wuhan, China, and on March 11, 2020, the World Health Organization declared it a pandemic and an emergency threatening public health^{1,2}. The most common clinical symptoms of the disease are fever and cough, along with other non-specific symptoms including dyspnea, headache, muscle aches, and fatigue³. The severity of the disease ranges from an asymptomatic condition to acute respiratory syndrome, organ failure, and even death in critical cases¹⁻⁴. Laboratory findings are also variable in this disease. Normal or low white blood cell counts, lymphopenia or thrombocytopenia, prolonged thromboplastin, and elevated C-reactive protein levels have been reported in COVID-19 patients^{5,6}.

Early detection of severe cases of COVID-19 is very important for all health care systems to predict the need for ICU beds and ventilators and to improve patient prognosis in the pandemic situation where medical resources face shortages⁴. Hence, researchers

have always been seeking solutions for the early detection of severe cases. To this end, patients' clinical symptoms, laboratory findings, and imaging can be helpful. Various studies have used lymphocyte counts and CRP levels, as well as the severity of pulmonary involvement in CT scans, to diagnose and determine the severity of the disease³⁻⁵.

In some countries, such as China and Italy, the use of respiratory symptoms and fever along with lung CT scans, leukopenia or lymphopenia, and high CRP has been recommended for patient screening². On the other hand, lung CT scans are used to diagnose and determine the severity of the disease in many international protocols³⁻⁵. Given that polymerase chain reaction testing (RT-PCR) may not be available in emergencies, and as lung CT scans are very expensive and can impose radiation and future complications for patients, the severity of pulmonary involvement due to COVID-19 might be determined through simpler and more accessible tests. Accordingly, the present study aimed to determine the relationship between lymphocyte counts and CRP levels and the severity of pulmonary involvement in CT scans of patients with

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pneumonia caused by COVID-19 in Imam Reza Hospital of Mashhad University Of Medical Sciences in 2020.

METHODS

During the COVID-19 Epidemic in Iran, with randomized sampling, 165 COVID-19 patients entered the study based on clinical symptoms and positive PCR or CT scan findings at Imam Reza Hospital in Mashhad from March to May 2020, and a cross-sectional study was designed (This study was approved by the Ethics Committee of Mashhad University of Medical Sciences, with the code of ethics IR.MUMS.REC.1399.093). The inclusion criterion was a definitive diagnosis of COVID-19 based on clinical findings, plus PCR results, or positive lung CT scan findings on the first day of hospitalization. On the other hand, the exclusion criteria were defective information in patients' records, taking glucocorticoids or immunosuppressive drugs, undergoing chemotherapy, having an autoimmune disease, blood malignancies, osteomyelitis, and chronic infections. The information of patients including age, sex, underlying disease, and laboratory findings such as CBC, absolute lymphocyte counts (counted by standard CymaxKy21 device) and CRP levels (measured by BT3000 biochemical auto analyzer device) was extracted and recorded in checklists.

After collecting information, two radiologists from the university's faculty were asked to assist to confirm the percentage of pulmonary involvement. The six lobes of each lung were examined and scored 0 - 4 based on the percentage of involvement. The total CT score was the total score of the individual's lobes from 0 to 24, based on which the patients were divided into 4 groups (Figure 1).

Statistical analysis

The variables were described using central tendency (percentage and frequency, mean and standard deviation), and the data were analyzed (after assessing the normality condition for quantitative variables) through ANOVA and chi-square statistical tests. The Pearson correlation coefficient and the ROC curve were also used to determine the relationship between the two quantitative variables. The significance level in this study was considered less than 0.05.

RESULTS

In this study, after excluding 40 patients due to the lack of qualification or having defects in their medical records, the data were collected from 125 patients with Covid-19, of whom 79 (63.2%) were male and 46

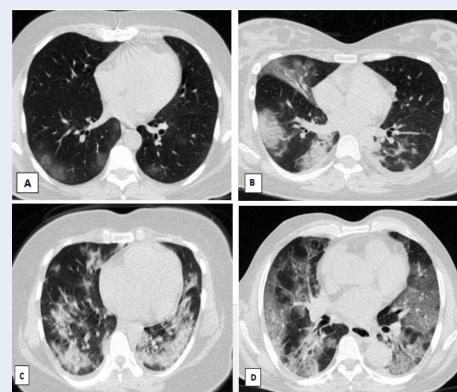


Figure 1: The severity of lung involvement is based on high-resolution computed tomography. (A) Minimal involvement (1 - 25 %) Patchy ground glass opacities (GGO) in lower lobes. (B) Mild involvement (26 - 50 %) Ground glass opacities (GGO) in right middle lobe and consolidation in right lower lobe. (C) Moderate involvement (51 - 75 %) Multifocal consolidation and small ground glass opacities (GGO) in both lower lobes and right middle lobe. (D) Severe involvement (76 - 100 %). Diffuse ground glass opacities (GGO) in both lower and middle lobes

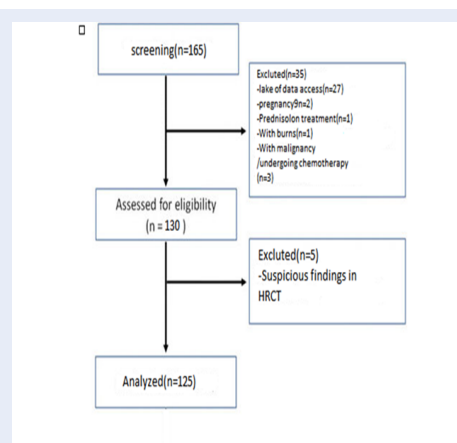


Figure 2: Flow diagram of the patients included in study.

(36.8%) were female. The mean age of the participants was 59.37 ± 1.5 years (with a minimum age of 26 and a maximum of 93 years). Besides, the mean lymphocyte count in the total number of patients was $1091/17 \pm 52$ cells/ μ l (with a minimum of 154 cells/ μ l and a maximum of 2600 cells/ μ l) and the mean CRP level of the patients was 99.36 ± 8.8 mg/l (at least 0.2 mg/l and at most 423 mg/l) (Figure 2). Patients were divided into 4 groups based on the lung involvement in

Table 1: Demographic information related to study participants

Group (The severity of lung involvement is based on HRCT)	Mild (%) N	Moderate (%) N	Sever (%) N	Very Severe (%) N	Total (%) N	P-value
Sex						
Male (%) N	(51/7) 15	(65/7) 23	(68/8) 22	(65/5) 19	(63/2) 79	0.526*
Female (%) N	(48/3) 14	(34/3) 12	(31/2) 10	(34/5) 10	(36/8) 46	
Lymphopenia (× 10⁹/L)						
> 1100 (%) N	(31) 9	(51/4) 18	(78/1) 25	(69) 20	(57/6) 72	0.001
< 1100 (%) N	(69) 20	(48/6) 17	(21/9) 7	(31) 9	(42/4) 53	
CRP (mg/L)						
> 100 (%) N	(20/7) 6	(22/9) 8	953/1) 17	975/9) 22	(42/4) 53	0.001
< 100(%) N	(79/3) 23	(77/10) 27	(46/9) 15	(24/1) 7	(57/6) 72	
AGE (year) (mean ± SD)	58/37 ± 18/28	55/76 ± 16/47	60/25 ± 15/64	63 ± 12/08	59/22 ± 15/84	0/325**
Lymphocyte count (× 10 ⁹ /L) (mean ± SD)	1468/9 ± 617/55	1083/9 ± 423/79	912/8 ± 445/7	921/1 ± 456/4	1091/7 ± 529/5	0/001
CRP level (mg/L) (mean ± SD)	41/96 ± 53/34	74/79 ± 76/56	128/11 ± 89/96	155/87 ± 86/79	99/63 ± 88/74	0/001
Total	(23/2) 29	(28) 35	(25/6) 32	(23/2) 29	(100) 125	

* Chi 2 test, ** Anova Test (Post hoc)

Table 2: Predicting the severity of lung involvement based on the variables of lymphocyte count and CRP (Linear regression).

Variable	β	SD	*β	Statistics of t	P-value
Lymphocyte count (× 10 ⁹ /L)	- 0/004	0/001	- 0/345	- 4/078	0/001
CRP level (mg/L)	0/038	0/006	0/505	6/486	0/001
Lymphopenia** < 1100 (× 10 ⁹ /L)	4/737	1/163	0/351	4/075	0/001
CRP ** >100 (mg/L)	6/689	1/074	0/497	6/226	0/001

*Pearson correlation coefficient; **Odds Ratio

CT scan. 29 patients (23.2%) were in the mild involvement group, 35 ones (20%) in the moderate involvement group, 32 patients (25%) in the severe involvement group, and 29 ones (23.2%) in the very severe involvement group. Another classification was also performed and the patients were divided into two groups of lymphocyte count < 1100×10⁹/L and lymphocyte count > 1100×10⁹/L, and CRP <100 mg/L and CRP >100 mg/L. **Table 1** shows demographic information of the patients in each group.

The results of the present study showed that the prevalence of lymphocytes < 1100×10⁹/L and CRP >100 mg/L was higher in patients with severe and very se-

vere lung involvement than in those with mild and moderate involvement, which is statistically significant (p < 0.001). The comparison of the groups in terms of the difference between the mean absolute number of lymphocytes and the CRP levels using the ANOVA and post hoc showed that the patients with severe and very severe lung involvement had fewer lymphocytes (p < 0.001) and higher CRP levels (p < 0.001) than other groups (**Figures 3 and 4**).

The results of the Pearson correlation analysis (after normality assessment) used to examine the relationship between absolute lymphocyte count and CRP levels and the patients' scores of lung involve-

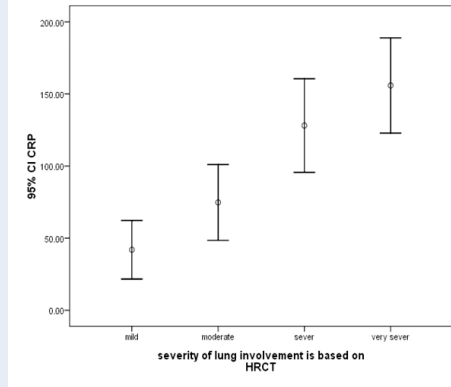


Figure 3: Comparison of mean CRP levels between groups of patients with pneumonia caused by Covid 19 virus with varying severity of lung involvement.

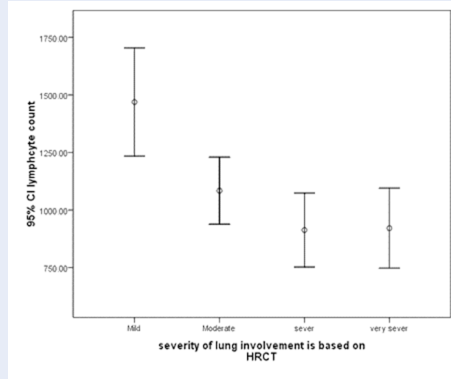


Figure 4: Comparison of the average absolute number of lymphocytes between groups of patients with pneumonia caused by the Covid 19 virus with different severity of lung involvement.

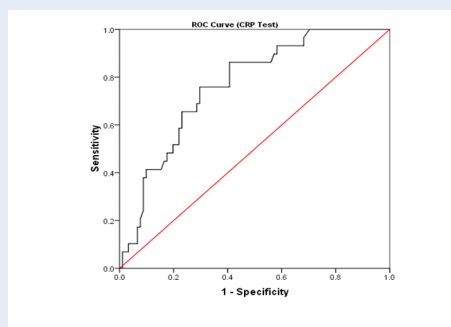


Figure 5: ROC diagram determining the diagnostic value of laboratory test CRP levels in diagnosing the severity of pulmonary involvement in patients with pneumonia caused by the Covid virus 19.

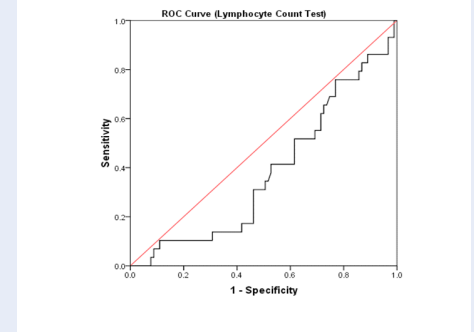


Figure 6: ROC diagram determining the diagnostic value of a laboratory test counting the number of lymphocytes in the diagnosis of pulmonary involvement in patients with pneumonia caused by the Covid virus 19.

ment in HRCT indicated a significant negative correlation between the absolute number of lymphocytes and the CT scan findings so that increased lung involvement in HRCT was associated with decreased absolute lymphocyte count ($p < 0.001$). On the contrary, there was a positive correlation between the severity of pulmonary involvement and the CRP levels. In other words, an increased percentage of pulmonary involvement in HRCT led to an elevated CRP level ($p < 0.001$). The results of linear regression analysis (after making the assumptions) also showed that absolute lymphocyte count and CRP levels were the factors used to predict the severity of lung involvement based on HRCT in patients with pneumonia caused by Covid-19 (Table 2).

In this study, the ROC curve (Receiver Operating Characteristic) was used to determine the diagnostic value of laboratory tests such as blood lymphocyte count and CRP in predicting the severity of pulmonary involvement in patients with pneumonia caused by COVID-19. Considering HRCT as a standardized test in blood lymphocyte counting, we found the area under the ROC curve to be 0.38 with a confidence interval of 0.27 - 0.49, showing the lack of accuracy and strength of this test to diagnose the severity of lung involvement in COVID-19 patients with pneumonia.

The results of the diagnostic value analysis for the CRP test showed that the area under the ROC curve was 0.76 with a confidence interval of 0.67 - 0.85. Thus, for the CRP = 98 mg/L, the highest sensitivity and the highest specificity were 72% and 71%, respectively, suggesting that the CRP measurement test could be an acceptable test for predicting the severity of lung

involvement in patients with COVID-19 pneumonia (Figures 5 and 6).

DISCUSSION

Based on the results of this study, which aimed to determine the relationship between lymphocyte counts and CRP levels and the lung CT scan findings of 125 patients with pneumonia caused by COVID-19, the patients with severe pulmonary involvement due to COVID-19 pneumonia had a higher prevalence of lymphopenia and a positive CRP than those with mild and moderate lung involvement. Guan *et al.* examined the data from 1,099 cases of COVID-19 in China and found that 83.2% of patients had lymphocytopenia and 60.7% of the patients had increased CRP⁷⁻⁹. Similarly, Gemin Zhang stated in his study that lymphocyte percentage < 10%, and CRP > 150 mg/L were associated with severe coronavirus pneumonia in 2019⁷.

Lymphopenia has been reported in various viral diseases, such as SARS, where the main mechanism of lymphopenia might be an increase in vascular permeability, but its mechanism is unknown in patients with COVID-19¹⁰⁻¹². However, the results obtained in the present study could be justified based on four possible pathophysiological mechanisms that researchers have considered for the lack of lymphocytes in these patients.

In this study, a significant negative correlation was found between the absolute number of lymphocytes and the intensity of lung CT scan findings in patients with COVID-19 pneumonia. Contrary to this finding, the correlation between CRP and COVID-19 pneumonia severity was positive. Analysis of clinical data from 115 patients with pneumonia caused by COVID-19 yielded similar results in studies by Jiheng Liu and Liu Y in China. They found that lymphopenia was associated with pneumonia severity and CRP levels¹⁰⁻¹³. In line with this finding, the results of a meta-analysis by Qianwen Zhao on the latest COVID-19 studies from December 2019 to March 22, 2020, in English and Chinese, showed that patients with severe pulmonary involvement due to COVID-19 pneumonia had higher lymphopenia and were at a three-fold increased risk of intensive COVID-19 pneumonia compared to the non-severe group¹⁴.

The results of a retrospective study by Wu *et al.*, who analyzed the possible risk factors for ARDS and death among 201 patients with COVID-19 pneumonia in Wuhan, China, showed a significant relationship between lymphopenia and increased CRP and acute respiratory distress syndrome¹⁵. In their studies, Evangelos Terpos and L. Wang also reported that pulmonary

nodule diameter in HRCT and the incidence of severe COVID-19 infection had a positive correlation with CRP levels^{16,17}.

The CRP level is associated with the level of inflammation and indicates the activation of the immune system, penetration of lymphocytes, use of immune molecules, and prevalence of inflammation, and is clinically considered one of the early signs of nosocomial infections in COVID-19 patients^{4,18,19}. In the early stages of the disease, CRP can reflect the severity of the disease and be used as an important indicator for early diagnosis and control of COVID-19²⁰⁻²².

In this research, the results of examining the diagnostic value of laboratory tests to measure the number of blood lymphocytes and CRP levels for determining the severity of pulmonary involvement in patients with pneumonia caused by COVID-19 (standard HRCT test) using the ROC curve (Receiver Operating Characteristic) showed that the CRP measurement test, unlike the blood lymphocyte count test, could be acceptable for diagnosing the severity of lung involvement in COVID-19 pneumonia patients.

A similar result was found by Wei Chen *et al.*, showing that the correlation between plasma CRP levels and COVID-19 pneumonia severity in HRCT (independent of age and lymphocyte count) was positive. They also analyzed the CRP diagnostic function using the ROC curve and compared it with HRCT intensity in COVID-19 pneumonia. The area under the curve was 0.898, and the P value was < 0.001. In another study by Chaochao Tan to analyze the CRP diagnostic function in predicting severe COVID-19 pneumonia, the area under the ROC curve was found to be 0.87, and the P value was < 0.001. The results of both studies show the good accuracy and strength of CRP in predicting the severity of COVID-19 pneumonia in the early stages of the disease, which is consistent with the results of the present study^{23,24}.

Although previous studies introduced CT scans as a quick and accurate way of screening for lung infections with unique diagnostic benefits, due to the limitations of performing CT scans under pandemic conditions including high cost, requirement for specialist staff, and risks associated with patient transportation and examination, the CRP assay test can be an acceptable test to diagnose the severity of lung involvement in patients with pneumonia¹⁷. There are limitations to undergoing CT scans in COVID-19 pandemic conditions, including high cost, the need for specialized staff, and the risks associated with transporting and examining patients. Alternatively, the CRP measurement test can be an acceptable test to diagnose the

severity of lung involvement in patients with COVID-19 pneumonia^{14,15,17}.

One of the weaknesses of the present research is the small sample size and the collection of data from only one hospital, which can lead to bias in the results. In the end, more extensive studies on other laboratory indices and inflammatory factors are recommended to predict the severity of CT scan involvement in patients with COVID-19. Optimal resource utilization is also recommended.

CONCLUSIONS

In this study, a significant positive correlation was found between CRP levels and the severity of pneumonia caused by COVID-19. The CRP measurement test can also be an acceptable test for predicting the severity of lung involvement in COVID-19 pneumonia patients.

ABBREVIATIONS

ANOVA: Analysis of Variance, **ARDS:** Acute Respiratory Distress Syndrome, **CBC:** Complete Blood Count, **COVID-19:** Coronavirus Disease 2019, **CRP:** C-reactive protein, **CT scan:** Computed Tomography scan, **HRCT:** High-Resolution Computed Tomography, **ICU:** Intensive Care Unit, **PCR:** Polymerase Chain Reaction, **ROC curve:** Receiver Operating Characteristic curve, **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2, **SPSS:** Statistical Package for the Social Sciences

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AUTHOR'S CONTRIBUTIONS

MP, EB, HF designed and implemented the study, performed analysis, interpreted the data, and contributed to drafting the manuscript. PL and MF interpreted the data, drafted and revised the manuscript. SSH and MP extracted the data and contributed to the data management. All authors read and approved the submitted manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences, with the code of ethics IR.MUMS.REC.1399.093.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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