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# Association between C-Reactive Protein Test Result and Clinical Characteristics in Patients with COVID-19

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## ABSTRACT

**Background and objectives:** In coronavirus disease 2019 (COVID-19), elevated serum levels of C-reactive protein (CRP), a marker of systemic inflammation, are commonly observed. We aimed to investigate the associations between CRP test results and clinical characteristics in patients with COVID-19.

**Method**: In this cross-sectional study, data from 399 patients with COVID-19 were collected through a census method. The patients were divided into a CRP-positive group (n=335) and a CRP-negative group (n=64). Demographical data, laboratory findings, clinical characteristics, and history of some underlying diseases were compared between the two groups. All analyses were carried out in SPSS (version 21).

**Results:** The frequency of hypertension was 40.1% among the study population, 42.4 % among CRP-positive patients, and 28.1% among CRP-negative patients. Diabetes and heart disease were the most common comorbidities among the patients. Dyspnea (60.4%), fever (52.7%), fatigue (45.4%), and dry cough (40.1%) were the most commonly observed symptoms. The mean duration of hospitalization was 8.14±6.18 days, and the mean duration of intensive care unit stay was 9.09±9.41 days. Moreover, CRP positivity was significantly associated with hypertension, immunosuppressive therapy, and higher duration of hospitalization ($p$<0.05).

**Conclusion:** Pre-existing hypertension, diabetes, and heart disease with the coincidence of some clinical symptoms are associated with higher levels of CRP in COVID-19 patients, which results in longer hospitalization.

**Keywords:** COVID-19 Testing, SARS-CoV-2, C-reactive protein.

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) has resulted in a global catastrophe. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the disease, which can target both the respiratory tract and the kidneys (1). The identification of effective laboratory biomarkers and diagnostic parameters can help determine the severity and prognosis of COVID-19 in the affected patients. Among laboratory factors, C-reactive protein (CRP) is an acute-phase protein that increases rapidly during infection. A higher level of CRP was observed in COVID-19 patients with severe illness (2). Nonetheless, for the assessment of host inflammatory status and identification of viral infection in other pathologies, acute-phase proteins, such as CRP can provide more vital data for managing clinical diagnosis and therapy (3–5).

Several conditions could elevate CRP, including acute and chronic reactions, which can be infectious or non-infectious etiologies (2). Elevated CRP is not common in most viral infections, but a study of 1,099 COVID-19 patients conducted in China showed that 60.7% of subjects had CRP levels above 10 mg/L (6). A study of 1,834 COVID-19 patients in Italy and the United Kingdom also found a mortality rate of 15% for patients with CRP levels below 40.0 mg/L compared with 31.9% for patients with CRP levels above 40.0 mg/L (7). The use of CRP as a biomarker in COVID-19 may present a quick and accessible tool for clinical management, especially in patients with underlying diseases. Pre-existing comorbidities such as cardiovascular disease, diabetes, and hypertension have been reported to be associated with the severity of COVID-19 and serious complications including stroke, septic complications, and even death (2,3,8,9). Higher CRP levels could be a valuable indicator of COVID-19 severity (5), which could also help the timely initiation of treatment. In this regard, we performed a study to investigate the association between CRP and the clinical characteristics of patients with COVID-19.

## MATERIALS AND METHODS

This cross-sectional study was performed on 399 COVID-19 patients aged 21-93 years who were referred to the Razi Educational and Medical Center in Rasht (Iran) from March 2020 to September 2020. Data were collected through a census method. According to the result of the CRP test, patients were divided into two groups: patients with positive CRP results (n=335) and negative CRP results (n=64). COVID-19 was confirmed by a positive real-time polymerase chain reaction (RT-PCR). Patients without complete information were excluded from the study. All study protocols were performed in accordance with the relevant guidelines and regulations. The Ethics Committee of Guilan University of Medical Sciences approved this research project (IR.GUMS.REC.1399.377), and informed consent was obtained from all subjects and/or their legal guardian(s). Demographical data and clinical characteristics including gender, duration of hospitalization, duration of stay in the intensive care unit (ICU), intubation, and laboratory factors including CRP, blood sugar (BS), blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, polymorph nuclear leukocytes (PMNs) count, lymphocyte count, prothrombin time (PT), partial thromboplastin time (PTT), and arterial blood gas (ABG) analysis were recorded. Clinical symptoms, presence of underlying diseases, outcomes, and mortality rate were also recorded.

The biochemical parameters were analyzed using an auto-analyzer (Mindray BS-800, UK; ParsAzmoon, Iran & Biorexfars, Iran). Hematological parameters were evaluated using a hematology analyzer (Sysmex KX-21N, Japan & Caretium XC-A30, China). Moreover, blood gas was analyzed (ABL9 blood gas analyzer, USA), and coagulation test was performed using a coagulometer (Sysmex CA 620, Japan; Baharafshan, Iran). A CRP level of ≥6 mg/L and <6 mg/L was identified as positive and negative, respectively (Biorexfars BXC0382, Iran)

Categorical variables were described as frequency and percentage. The frequency of underlying diseases in CRP-positive and -negative groups were evaluated using the Mann–Whitney U test and Fisher's exact test. In addition, the chi-square and Mann–Whitney U test were applied to determine the frequency of patient outcomes among the two study groups. Statistical analysis was performed using the IBM SPSS software (version 21)

with a significant of 0.05.

## RESULTS

The mean age of the patients was 60.89±15.91 years. Of 399 COVID-19 patients, 245 (61.4%) were male and 154 (38.6%) were female. A total of 335 (84%) patients had positive CRP results and 64 patients (16%) had negative CRP results. The most frequent underlying diseases were hypertension, diabetes, cardiovascular diseases, and hyperlipidemia. Moreover, dyspnea (60.4%), fever (52.7%), fatigue (45.4%), dry cough (40.1%), chills (36.3%), and myalgia (23.6%) were the most common clinical symptoms among the patients. The mean duration of hospitalization, ICU stay, and intubation was 8.14±6.18, 9.09±9.41, and 6.63±9.13 days, respectively. The mean mortality rate was 24.8% (Table 1).

**Table 1- The frequency of clinical characteristics among patients with COVID-19**

| Variables | Number | Percentage |
|---|---|---|
| Anosmia | 11 | 2.8% |
| Ageusia | 4 | 1.0% |
| Hemoptysis | 2 | 0.5% |
| Heart disease | 99 | 24.8% |
| Diabetic Mellitus | 131 | 32.8% |
| Hypertension | 160 | 40.1% |
| Hyperlipidemia | 73 | 18.3% |
| Cerebrovascular accident | 20 | 5.0% |
| Chronic obstructive pulmonary disease | 7 | 1.8% |
| Chronic kidney disease | 15 | 3.8% |
| End-stage renal disease | 11 | 2.8% |
| Asthma | 17 | 4.3% |
| Cancer | 17 | 4.3% |
| Cortone consumption | 6 | 1.5% |
| Immunosuppressive therapy | 5 | 1.3% |
| Dyspnea | 241 | 60.4% |
| Fever | 208 | 52.7% |
| Chills | 145 | 36.3% |
| Dry cough | 160 | 40.1% |
| Myalgia | 94 | 23.6% |
| Productive cough | 61 | 15.3% |
| Sore throat | 6 | 1.5% |
| Fatigue | 181 | 45.4% |
| Headache | 27 | 6.8% |
| Nausea | 84 | 21.1% |
| Vomit | 70 | 17.5% |
| Diarrhea | 48 | 12.0% |
| Loss of appetite | 104 | 26.1% |
| Abdominal pain | 31 | 7.8% |
| Mental status changes | 40 | 10.0% |
| Dizziness | 2 | 0.5% |
| Chest pain | 84 | 21.1% |
| Death outcome | 99 | 24.8% |
| ICU admission | 55 | 13.8% |
| Need for intubation | 63 | 15.8% |

**Table 2- Laboratory findings among the study population**

| Variables | Mean ± standard deviation |
|---|---|
| BS | 164.13±91.12 |
| BUN | 24.45±17.71 |
| Cr | 1.55±1.44 |
| AST | 56.74±101.03 |
| ALT | 48.41±118.94 |
| ALP | 287.29±631.15 |
| ESR | 53.45±27.49 |
| WBC | 8.45±5.20 |
| PMN | 74.87±18.11 |
| Lymphocyte | 18.54±11.86 |
| Artery blood gas pH | 7.55±3.89 |
| $PaCO_2$ | 45.35±12.89 |
| $PaO_2$ | 61.73±46.06 |
| $HCO_3$ | 24.17±7.78 |
| $O_2$ saturation | 71.24±22.60 |
| PT | 12.91±2.09 |
| INR | 1.15±0.52 |
| PTT | 33.56±8.38 |
| CRP | 80.57±74.86 |

Table 2 shows the mean level of hematological and biochemical parameters in the patients.

BS: blood sugar; BUN: blood urea nitrogen; Cr: creatinine; AST: aspartate amino transferase; ALT: alanin amino transferase; ESR: erythrocyte sedimentation rate; WBC: white blood cell; PMN: polymorph nuclear leukocytes; PT: prothrombin time; PTT: partial thromboplastin time

Hospitalization duration, hypertension, and immunosuppressive therapy were significantly associated with CRP positivity in patients with COVID-19. There was no significant association between CRP level and mortality, ICU admission, and the need for intubation (Table 3).

**Table 3- Comparison of the frequency of comorbidities and patient outcome between two study groups**

| Variables | CRP-negative N (%) | CRP-positive N (%) | P-value |
|---|---|---|---|
| Anosmia | 2 (3.1%) | 9 (2.7%) | 0.692** |
| Ageusia | 0 (0.0%) | 4 (1.2%) | >0.999** |
| Hemoptysis | 0 (0.0%) | 2 (0.6%) | >0.999** |
| Heart disease | 17 (26.6%) | 82 (24.5%) | 0.723* |
| Diabetic Mellitus | 19 (29.7%) | 112 (33.4%) | 0.559* |
| Hypertension | 18 (28.1%) | 142 (42.4%) | 0.033* |
| Hyperlipidemia | 13 (20.3%) | 60 (17.9%) | 0.649* |
| Cerebrovascular accident | 4 (6.3%) | 16 (4.8%) | 0.542** |
| Chronic obstructive pulmonary disease | 2 (3.1%) | 5 (1.5%) | 0.312** |
| Chronic kidney disease | 1 (1.6%) | 14 (4.2%) | 0.483** |
| End-stage renal disease | 2 (3.1%) | 9 (2.7%) | 0.692** |
| Asthma | 2 (3.1%) | 15 (4.5%) | >0.999** |
| Cancer | 4 (6.3%) | 13 (3.9%) | 0.495** |
| Croton consumption | 2 (3.1%) | 4 (1.2%) | 0.248** |
| Immunosuppressive therapy | 3 (4.7%) | 2 (0.6%) | 0.031** |
| Death | 16 (25.0%) | 83 (24.8%) | 0.970* |
| ICU admission | 8 (12.5%) | 47 (14.0%) | 0.745* |
| Need for intubation | 12 (18.8%) | 51 (15.2%) | 0.478* |
| Hospitalized duration | 7.28±5.52 | 8.30±6.29 | 0.049** |
| Duration of stay in ICU | 8.25±4.03 | 9.23±10.07 | 0.606** |
| Duration of intubation | 7.25±7.35 | 6.49±9.56 | 0.783** |

*** Chi-square test ** Fisher's exact test**

## DISCUSSION

In the present study, the association of clinical characteristics of hospitalized patients with COVID-19 and CRP level was studied. It is well-established that CRP levels increase during inflammatory events (10). This protein can activate the complement system and increase phagocytosis by binding to microorganisms (11,12). Serum CRP levels increase during inflammatory responses (13). Liu et al. found that severe COVID-19 patients expressed significantly higher CRP levels than their non-severe counterparts (14). A meta-analysis by Sahu et al. indicated that CRP levels remained high in expired patients, indicating the potential of CRP as an important biomarker for mortality (15). As reported in previous studies, elevated CRP levels can be an early marker of COVID-19 severity. Systemic inflammation is strongly associated with critical illness in COVID-19 patients (16,17). Previous studies have also shown that CRP is associated with extra-pulmonary disease in COVID-19, and there is a correlation between CRP level and myocardial injury in multiple series (18,19).

Our results indicated that cardiovascular complications and diabetes were the most comorbidities in both CRP-positive and -negative CRP COVID-19 patients. In line with our results, cardiovascular complications and hypertension were frequently reported in patients with COVID-19 (20–22). The present study showed that dyspnea, fever, fatigue, dry cough, and chills were the most common clinical symptoms among patients with COVID-19. Similar to our findings, the results of a meta-analysis study showed that fever in 81.2% of cases, cough in 58.5% of cases, and fatigue in 38.5% of cases were the most frequent symptoms among SARS-CoV-2 infected patients (23). In some studies, fever was reported as the most common symptom in patients with COVID-19, but not all patients had fever (24,25). These symptoms usually were accompanied by elevated CRP levels at the early stages.

In our study, no significant association was found between CRP and death in COVID-19 patients. However, CRP-positive patients had a longer hospital stay. A study by Lentner et

al. illustrated a positive correlation between the CRP levels of patients with COVID-19 and death as well as the longer duration of hospitalization (26). In addition to CRP, among laboratory parameters, ESR is another inflammatory indicator that becomes elevated in patients with COVID-19, which could also be used as a predictor of disease severity. As reported in some studies, it has been suggested that the levels of interleukin-6, tumor necrosis factor-α, ESR, and CRP could be used for predicting the severity of COVID-19 (27,28). In the present study, the frequency of ICU administration was only 13.8%. This may be related to the limited ICU capacity of the hospital that pushed clinicians to admit patients requiring ICU admission into other wards.

## CONCLUSION

Our findings indicate that CRP positivity is associated with longer hospitalization in patients with COVID-19. Moreover, hypertension, diabetes, and heart disease are the most common comorbidities in CRP-positive patients. It can be concluded that the main symptoms of COVID-19 can play a vital role in the early diagnosis and prevention of disease transmission.

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## DECLARATIONS

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### Ethics approvals and consent to participate

The Ethics Committee of Guilan University of Medical Sciences approved this research project (ethical approval code: IR.GUMS.REC.1399.377), and informed consent was obtained from all subjects and/or their legal guardian(s).

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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