Cardiopulmonary Medicine

Brief Report

Jacob Lentner, OMS III*, Taylor Adams, OMS IV, Valene Knutson, OMS III, Sarah Zeien, OMS IV, Hassan Abbas, OMS III, Ryan Moosavi, OMS III, Chris Manuel, OMS III, Thomas Wallace, MD, Adam Harmon, MD, Richard Waters, MD, Samuel Ledford, MD, Rajakrishnan Vijayakrishnan, MD, Nikhil Jagan, MD, Nezar Falluji, MD, Michael DelCore, MD, Curt Bay, PhD and Sunny Jhamnani, MD

C-reactive protein levels associated with COVID-19 outcomes in the United States

https://doi.org/10.1515/jom-2021-0103
Received April 5, 2021; accepted August 20, 2021;
published online September 30, 2021

Abstract

Context: COVID-19 caused a worldwide pandemic, and there are still many uncertainties about the disease. C-reactive protein (CRP) levels could be utilized as a prognosticator for disease severity in COVID-19 patients.
Objectives: This study aims to determine whether CRP levels are correlated with COVID-19 patient outcomes and length of stay (LoS).
Methods: A retrospective cohort study was conducted utilizing data obtained between March and May 2020. Data were collected by abstracting past medical records through electronic medical records at 10 hospitals within CommonSpirit Health. Patients were included if they had a positive COVID-19 test from a nasopharyngeal swab sample, and if they were admitted and then discharged alive or had in-hospital mortality and were ≥18 years. A total of 541 patients had CRP levels measured and were included in this report. Patient outcome and LoS were the endpoints measured.
Results: The 541 patients had their CRP levels measured, as well as the demographic and clinical data required for analysis. While controlling for body mass index (BMI), number of comorbidities, and age, the first CRP was significantly predictive of mortality ($p<0.001$). The odds ratio for first CRP indicates that for each one-unit increase in CRP, the odds of death increased by 0.007. For LoS, the first CRP was a significant predictor ($p<0.001$), along with age ($p=0.002$). The number of comorbidities also predicted LoS ($p=0.007$), but BMI did not. The coefficient for the first CRP indicates that, for each one-unit increase in CRP, LoS increased 0.003 days.
Conclusions: The results indicate that there is a positive correlation between the CRP levels of COVID-19 patients and their respective outcomes with regard to death and LoS.

Keywords: C-reactive protein; COVID-19; mortality; outcomes.

***Corresponding author: Jacob Lentner**, OMS III, A.T. Still University – Kirksville College of Medicine, Kirksville, MO, USA; and 577 E. Baseline Road, Apt. 2011, Tempe, AZ 85283-1692, USA, E-mail: jakelentner2772@gmail.com
Taylor Adams, OMS IV**, Valene Knutson,** OMS III **and Sarah Zeien,** OMS IV, A.T. Still University – Kirksville College of Medicine, Kirksville, MO, USA
Hassan Abbas, OMS III**, Ryan Moosavi,** OMS III **and Chris Manuel,** OMS III, Midwestern University, Glendale, AZ, USA
Thomas Wallace, MD, Department of Cardiovascular Medicine, CHI St. Vincent Infirmary, Chicago, IL, USA
Adam Harmon, MD, Department of Cardiovascular Medicine, Sequoia Hospital, Redwood City, CA, USA
Richard Waters, MD, Department of Cardiovascular Medicine, St. Joseph Medical Center, Stockton, CA, USA
Samuel Ledford, MD, Department of Cardiovascular Medicine, CHI Memorial Hospital, Chattanooga, TN, USA
Rajakrishnan Vijayakrishnan, MD, Department of Cardiovascular Medicine, St. Joseph Hospital and Medical Center, Phoenix, AZ, USA
Nikhil Jagan, MD, Department of Pulmonary and Critical Care Medicine, CHI Health St. Francis, Grand Island, NE, USA
Nezar Falluji, MD, Department of Cardiovascular Medicine, CHI St. Joseph Hospital, Lexington, KY, USA
Michael DelCore, MD, Department of Cardiovascular Medicine, CHI Health Creighton University Medical Center – Bergan Mercy, Omaha, NE, USA
Curt Bay, PhD, A.T. Still University, Mesa, AZ, USA
Sunny Jhamnani, MD, Department of Cardiology, Chandler Regional Medical Center, Chandler, AZ, USA

C-reactive protein (CRP) is an acute-phase reactant that is produced by the liver in response to inflammation. It is commonly secreted under the influence of cytokines such as interleukin-6 and tumor necrosis factor-alpha. More specifically, a study including over 50,000 participants noted a significant association between elevated serum or plasma concentrations of CRP and ischemic vascular disease. The study demonstrated that the risk of ischemic heart disease and ischemic cerebrovascular disease was increased by a factor of 1.6 and 1.3, respectively, in persons

who had CRP levels above 3 mg per liter, as compared with persons who had CRP levels below 1 mg per liter [1].

Although an elevated CRP is not common in most viral infections, a study conducted in China with 1,099 COVID-19 patients demonstrated that 60.7% had CRP levels ≥10 mg/L [2]. Another study including 76 COVID-19 patients demonstrated that the hospital length of stay (LoS) averaged 20 days in patients with CRP levels ≥20.4 mg/L and 18 days in patients with CRP levels <20.4 mg/L [3]. Furthermore, a study of 27 COVID-19 patients found that CRP levels >20.4 mg/L were 83.0% sensitive and 91.0% specific when predicting severe COVID-19 infection [4]. A study of 1834 COVID-19 patients from Italy and the United Kingdom found that CRP levels ≥40.0 mg/L were associated with 31.9% mortality compared with 15.0% mortality in patients with CRP levels <40.0 mg/L [5]. None of these studies were conducted in the United States, so further investigation into the relationship between CRP and COVID-19 in the U.S. population is warranted. The aim of this study is to determine if the first CRP levels on hospital admission or the highest CRP are associated with mortality, length of hospital stay, and disposition in patients hospitalized with COVID-19.

Methods

This study was approved by the Dignity East Valley IRB (IRB number: EVR-20-510-114-66-17). It did not involve intervention of human patients; therefore, a clinical registry number was not indicated. Informed consent was deemed unnecessary and was waived per the IRB.

Study design

Data were abstracted retrospectively from the medical records of 10 hospitals within CommonSpirit Health (Chandler Regional Medical Center; Mercy Gilbert Medical Center; CHI Health Creighton University Medical Center; CHI Health St. Francis; CHI Memorial Hospital, Chattanooga; CHI St. Joseph Hospital, Lexington; CHI St. Vincent, Little Rock; Sequoia Hospital; St. Joseph's Hospital and Medical Center, Phoenix; and St. Joseph's Medical Center, Stockton), the second largest healthcare system in the United States. Patients were included if they: (1) had a confirmed positive COVID-19 test utilizing the polymerase chain reaction method from a nasopharyngeal swab sample; (2) were admitted and then discharged alive or died in the hospital between March 1, 2020 and May 31, 2020; and (3) were ≥18 years.

We evaluated the association of CRP level with: (1) mortality; (2) hospital LoS; and (3) patient disposition to home, long-term rehab facility, or hospice.

Data collection

Data were abstracted from electronic medical records, including admission history and physical notes, discharge summaries, and laboratory records during the patients' hospital stay.

Statistical analysis

Summary statistics are provided as means (standard deviations), counts (percentages), and medians (interquartile ranges). Standard errors and 95.0% confidence intervals are also reported, where appropriate. A generalized estimating equations approach was utilized to address clustering by hospital, and robust confidence intervals were calculated because a few patients were admitted more than one time. A binary logistic distribution link was utilized for mortality, a gamma distribution link for LoS because data were skewed, and a multinomial link for disposition. Spearman's rho (r_s) was utilized to estimate the correlation between first and highest CRP levels. An alpha of 0.05 was utilized as the criterion for statistical significance. SPSS version 27 (IBM Corp., Armonk, NY) was utilized for analyses.

Constructing models to predict LoS is complicated in the presence of significant mortality. The hospital stay may be terminated by death or by discharge alive. Patients who are not very sick will have a relatively short LoS, and this stay will increase as a function of how sick the patients are. However, the sickest patients may have a short LoS, terminating in death. In order to evaluate the potential impact of CRP on LoS, we conducted LoS analyses utilizing only the patients who were discharged alive.

Results

Dataset

Data from 865 patients were abstracted, and 541 had their CRP levels measured, as along with the demographic and clinical data required for analysis. Table 1 provides summary descriptive statistics for the analysis dataset, subdivided by patients who survived (n=445) and those who died (n=96). Aside from CRP levels, only age differed significantly across groups ($p<0.001$).

For analyses predicting mortality, LoS, and disposition, the first and highest levels of CRP were of primary interest. In all analyses, age, BMI, and the number of comorbidities were entered as covariates. Sex, race, and ethnicity were tested as covariates, but they altered the solutions only slightly, and none were significantly predictive of the outcomes (i.e., did not alter the confidence intervals or parameter coefficients), so they were removed. The first and highest CRP levels were correlated, $r_s=0.92$ ($p<0.001$), indicating they were substantially redundant for purposes of prediction. The results of the analyses utilizing these two variables differed only very slightly, so only the results utilizing first CRP are presented.

Mortality

Results for the analysis predicting patient mortality are provided in Table 2. While controlling for BMI, the number

Table 1: Demographic and clinical summary statistics.

Variable	Survived (n=445)	Died (n=96)
Age, years	56.8 ± 16.8	69.0 ± 13.1
Sex		
Male	233 (82.3)	50 (17.7)
Female	212 (82.2)	46 (17.8)
Race		
White	303 (83.0)	62 (17.0)
Black	41 (78.8)	11 (21.2)
American Indian/Alaska Native	32 (72.7)	12 (27.3)
Asian	18 (94.7)	1 (5.3)
Other/unknown	51 (83.6)	10 (16.4)
Ethnicity		
Hispanic/Latino	150 (84.7)	27 (15.3)
Not Hispanic/Latino	281 (82.4)	60 (17.6)
Unknown	14 (60.9)	9 (39.1)
Body mass index, kg/m^2	32.17 (8.57)	31.03 (8.69)
No. of comorbidities	2.0 ± 1.93	2.77 ± 2.04
First CRP	78.70 ± 85.56	132.63 ± 112.10
First CRP, median (IQR)	42.45 (11.90, 129.21)	127.01 (25.83, 210.22)
Highest CRP	101.63 ± 131.83	194.07 ± 144.22
Highest CRP, median (IQR)	57.70 (16.25, 155.25)	184.11 (43.03, 291.83)

The symbol ± is utilized for mean ± standard deviation. Parentheses are utilized for count (percentage) unless otherwise noted; IQR, interquartile range.

of comorbidities, and age, the first CRP was significantly predictive of mortality (p<0.001). Age also predicted mortality (p<0.001), but neither BMI nor the number of comorbidities were significant. The odds ratio for the first CRP indicates that for each one-unit increase in CRP, the odds of death increased by 0.007. For context, each 50-unit increase resulted in odds increasing by almost 42% (OR=1.42, 95% CI: 1.25–1.60), and for each 100-unit increase in CRP, the odds of death increased two-fold (OR=2.01, 95% CI: 1.57–2.56), while controlling for BMI, the number of comorbidities, and age.

Length of stay (LoS)

Parameter estimates for LoS are provided in Table 3. The first CRP was a significant predictor (p<0.001), along with age (p=0.002). The number of comorbidities also predicted LoS (p=0.007), but BMI did not. The coefficient for the first CRP indicates that for each one-unit increase in CRP, LoS increased 0.003 days; for each 50-unit increase, LoS increased by 0.16 days (95% CI: 0.10–0.21), and for each 100-unit increase in CRP, the LoS increased an average of 0.31 days, (95% CI: 0.20–0.42), while controlling for BMI, the number of comorbidities, and age.

Disposition

As shown in Table 4, disposition could be predicted by the number of comorbidities (p=0.002) and age (p<0.001); however, the first CRP did not appear to play a role.

Discussion

In this study, we found that CRP levels are predictive of mortality, independent of factors such as age, BMI, and comorbidities. The higher the patient's CRP level, the greater the chance the patient died. We also found a similar association between CRP levels and the length of stay in the hospital from admission to discharge. However, there was no significant association between CRP levels and disposition.

Although age was also a significant predictor of patient mortality, it does not discount the fact that CRP levels demonstrated a positive correlation with death. Similarly, the CRP level was not the only parameter that was statistically significant when evaluating LoS, but further research would need to be conducted to determine which parameter, if any, played the most significant role in prolonging LoS.

In COVID-19, the pathophysiology is underpinned by pulmonary and systemic inflammatory changes, as demonstrated by a study of 191 COVID-19 patients in which 75.0% demonstrated bilateral pulmonary infiltration, 71.0% had ground glass opacities, and 67.0% had a lactate dehydrogenase level >245 U/L [6]. CRP is an inflammatory marker, and the results of this study would suggest that the higher the CRP level in patients, the greater the severity of their disease, and the worse the patient outcomes.

Because higher CRP levels suggest greater systemic inflammation, future studies may be conducted to determine the effects of corticosteroids and/or other anti-inflammatory medications on patient outcomes [7]. However, the data analyzed in this study primarily focused on CRP as a predictor of COVID-19 outcomes, not treatment of the infection. Additionally, the sample of patients from the raw data who received dexamethasone was not large enough to determine its significance.

The previous studies referenced in the introduction [2–5] demonstrated a positive correlation with CRP levels,

Table 2: Prediction of mortality by BMI, the number of comorbidities, age, and the first CRP.

Parameter	Beta	SE	95% CI	Chi-Sq	p-Value	OR	95% CI
BMI	0.019	0.017	−0.014, 0.052	1.274	0.259	1.019	0.986, 1.054
Comorbidities	0.087	0.063	−0.036, 0.210	1.913	0.167	1.091	0.964, 1.234
Age	0.055	0.009	0.038, 0.072	38.303	<0.001[a]	1.057	1.038, 1.075
First CRP	0.007	0.001	0.005, 0.009	30.855	<0.001[a]	1.007	1.005, 1.009

BMI, body mass index; Chi-Sq, Wald chi-square; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; SE, standard error. [a]Denotes statistical significance.

Table 3: Prediction of LoS by BMI, number of comorbidities, age, and first CRP.

Parameter	Beta	SE	95% CI	Chi-Sq	p-Value
BMI	0.002	0.005	−0.007, 0.012	0.258	0.611
Comorbidities	0.073	0.027	0.020, 0.127	7.313	0.007[a]
Age	0.009	0.003	0.003, 0.015	9.535	0.002[a]
First CRP	0.003	0.001	0.002, 0.004	31.493	<0.001[a]

BMI, body mass index; Chi-Sq, Wald chi-square; CI, confidence interval; CRP, C-reactive protein; LoS, length of stay; SE, standard error. [a]Denotes statistical significance.

Table 4: Prediction of disposition by BMI, number of comorbidities, age, and first CRP.

Parameter	Beta	SE	95% CI	Chi-Sq	p-Value
BMI	0.001	0.014	−0.027, 0.029	0.004	0.949
Comorbidities	−0.172	0.057	−0.283, −0.061	9.279	0.002[a]
Age	−0.039	0.008	−0.054, −0.024	25.489	<0.001[a]
First CRP	0.000	0.001	−0.003, 0.002	0.094	0.759

BMI, body mass index; Chi-Sq, Wald chi-square; CI, confidence interval; CRP, C-reactive protein; SE, standard error. [a]Denotes statistical significance.

LoS, and disease severity/mortality, respectively. This study further supports these findings; however, the levels of CRP measured in this study were higher than those that were found in the previous studies. For example, the average CRP level of patients that died in the United Kingdom study was 115 mg/L[5] compared to 159.9 mg/L in this study. At this time, the possible etiology of this discrepancy is unknown to the authors, and further research may be warranted.

This study is necessary because it adds to this knowledge base by assessing each of these variables in one data set. The previous studies also were conducted with COVID-19 patients in China, the United Kingdom, and Italy, whereas this study had patients who were residents of the United States.

The tenet of osteopathic medicine that this study best demonstrates is "self-regulation." Earlier in the introduction, it was mentioned that CRP is an inflammatory marker. The body releases inflammatory products when it is attempting to fight off an infection, such as COVID-19. The results obtained in this study suggest that higher CRP levels are correlated with worse disease. This suggests that the body is attempting to self-regulate by producing more inflammatory products to eliminate the infection and heal itself.

Some limitations of this study include that this is a retrospective study and therefore is subject to confounding. Additionally, over two-thirds of the patients were white, thus this may not be a fair representation of all races.

Conclusions

The results indicate that there is in fact a positive correlation between the CRP levels of COVID-19 patients and their respective outcomes with regard to death and LoS. CRP could potentially be used as a prognostic indicator in COVID-19 patients as more is discovered about the virus. Clinically, significantly elevated CRP levels may be an indication for more aggressive treatment of COVID-19, yet further research would have to be conducted regarding different treatment methods and their effectiveness on reducing CRP levels and how the treatment correlates to COVID-19 patient outcomes.

Research funding: None reported.

Author contributions: T.A., V.K., S.Z., H.A., R.M., C.M., T.W., A.H., R.W., S.L., R.V., N.J., N.F., M.D., and C.B. provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; J.L. drafted the article or revised it critically for important intellectual content; S.J. gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that

questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests: None reported.

Ethical approval: This study was reviewed and approved by the Dignity East Valley IRB (IRB# EVR-20-510-114-66-17).

References

1. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. N Engl J Med 2008;359:1897–908.
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
3. Chen W, Zheng KI, Liu S, Yan Z, Xu C, Qiao Z. Plasma CRP level is positively associated with the severity of COVID-19. Ann Clin Microbiol Antimicrob 2020;19:18.
4. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol 2020;92:856–62.
5. Stringer D, Braude P, Myint PK, Evans L, Collins JT, Verduri A, et al. The role of C-reactive protein as a prognostic marker in COVID-19. Int J Epidemiol 2021;50:420–9.
6. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395: 1054–62.
7. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693–704.