ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 6, Issue – 1, Janaury - 2023, Page No. : 671 - 678

C-Reactive Protein (CRP) as a prognostic marker in COVID-19 patients - A cross-sectional comparative study

[1]Dr. M Anuradha, Professor, Microbiology, Malla Reddy Medical College for Women, Hyderabad.

[2]Dr. V Haritha, Associate professor, Microbiology, SRRITCD, Nallakunta, Hyderabad.

[3]Dr. K Abhilasha, Assistant professor, Microbiology, Osmania general hospital, Hyderabad.

[4]Dr. K Sneha Jigisha, Assistant professor, Microbiology, Gandhi general hospital, Hyderabad.

Corresponding Author: Dr. M Anuradha, Professor, Microbiology, Malla Reddy Medical College for Women, Hyderabad.

How to citation this article: Dr. M Anuradha, Dr. V Haritha, Dr. K Abhilasha, Dr. K Sneha Jigisha,"C-Reactive Protein (CRP) as a prognostic marker in COVID-19 patients - A cross-sectional comparative study", IJMACR-January - 2023, Volume – 6, Issue - 1, P. No. 671 - 678.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: In our study, we hypothesized that the CRP test can be used as an early predictor to detect COVID-19 patients' response to steroid treatment, thereby monitoring disease progression and outcome.

Aim: To evaluate the role of CRP as a prognostic marker in COVID -19 patients

Setting and design: A cross-sectional comparative study

Material and methods: Patients were divided into two groups- the first group received steroids and the second group did not receive steroids. A baseline CRP was done at the time of admission. Steroids given group was divided into CRP responders and CRP non-responders based on a 50% reduction in CRP levels and the outcome of the disease was compared. The group of patients who didn't receive steroids was monitored by Spo2 changes and disease outcomes.

Statistical analysis: Mean, Standard deviations, Chi-square test, P value, Odds ratio, ROC curve.

Results: Out of 178 patients, 71 (40%) were given steroids and 107(60%) were not given. In the steroids-given group, 70% of the patients were responders, and 30%were non-responders. P value was significant at <0.0435 among the responders and among the non-responders, the P value was <0. 002665. The area under the receptor operating curve was 0.911, showing that CRP had good sensitivity and specificity in monitoring the progression of the disease. The odds ratio was 0.77, (0.37, 1.63) at 95 % CI which proves that CRP responders had a reduced risk of death when compared to non-responders.

Conclusion: CRP levels can be used as a good marker to monitor the progression and outcome of the COVID-19 disease.

Keywords: COVID -19, CRP, Non-responders, Outcome, Responders, Steroids

Introduction

C-Reactive Protein (CRP) is one of the acute phase proteins appearing in blood within 6-10 hours of tissue damage and having a plasma half-life of 19 hours, which is constant regardless of the pathological process.[1] Mild elevation of CRP (10-20 mg/L) in COVID-19 disease can be diagnostic of mild viral disease, while moderate elevations (20-40 mg/L) may indicate some reversible tissue damage. But significantly elevated CRP levels (>100 mg/L) in COVID-19 patients more often have advanced tissue damage along with cytokine storm and multi-organ failure.[2]As shown in recent studies, treatment with glucocorticoids in COVID-19 patients has increased their lymphocyte count, reduced the CT scores, and CRP levels, and improved the coagulation function.[3] In a few retrospective studies, the authors concluded that a reduction in CRP levels by more than 50% within 72 hours of starting corticosteroid therapy had a positive correlation with a reduction in mortality rate. [(4,5)] With the above background, we propose to analyze CRP as a potential prognostic marker in evaluating the disease outcome.

Aim

To evaluate the role of CRP as a prognostic marker.

Objectives

1. To measure the CRP response after corticosteroid therapy among patients receiving steroid therapy, and correlate it with the disease outcome.
2. To evaluate the disease outcome among the CRP responders against that of non-responders.
3. To compare the CRP levels and disease progression among patients not given steroids for treatment, admitted for COVID-19 disease.

Material and methods

Type of Study: Prospective cross-sectional comparative study.

Place of study: Telangana Institute of Medical Sciences and Research (TIMS), Gachibowli, Hyderabad.

Duration of study: Six months (October 2021 to March 2022).

Inclusion criteria

1. Patients who are positive by RT-PCR/ Rapid Antigen Testing/ CT scan scoring for COVID-19 disease, are admitted to TIMS.
2. Patients receiving/ not receiving steroid therapy

Exclusion criteria

1. Patients dying within 48 hours of admission.

Methodology

COVID-19-positive patients (above 18 years) were considered for the study, confirmed either by RT-PCR or Rapid Antigen Testing (RAT) methods or by CT-scan scores. Informed consent was taken from the patients. Patients were divided into two groups- the first group received steroids and the second group did not receive steroids. For both groups, a baseline level of CRP was done within 48 hours of admission. CRP levels were retested for the first group (receiving steroids) around 72 hours after giving steroids. This group was again divided into two sub-groups: CRP responders and CRP non-responders. Patients were considered to be CRP responders if their CRP levels are reduced by at least 50% within 72 hours after treatment, and CRP non-responders if their CRP levels did not reduce. The outcome of disease among both the sub-groups was compared clinically by CRP estimation. CRP levels were

analyzed after 72 hours of the first CRP estimation in the steroids-not given group to correlate with the disease outcome. The clinical progression of the patients who did not receive steroids was monitored by SpO_2 changes and disease outcome[4]. CRP testing was done by the immunoturbidimetry method.

Statistical analysis

- All data were analyzed using IBM SPSS software version 27.0.
- Demographic variables about age, gender, and any co-morbid conditions were analyzed by using percentages, standard deviations, and mean values.
- Chi-square test and P-value calculation (less than 0.05 level of significance $p< 0.05$) was done to know the significance of the difference between the sub-groups of CRP responders and non-responders.
- Receiver Operator Characteristic (ROC) curve analysis was done to determine the discriminative power (Area Under Curve or AUC) of CRP as a good diagnostic test.
- ODDS ratio was calculated to correlate the mortality rate with CRP response.
- Mean of CRP was done for the group not receiving steroids for correlation with disease progression.

Results

A total of 178 patients were enrolled in our study. Male preponderance was seen with 61% of them being males. 71(40%) patients were included in the steroids-given group and 107(60%) of the patients in the steroids not given group. Table 1 shows the split of male and female patients who were categorized into steroids given and steroids not given groups.

Table 1: Total number of patients enrolled in the study, categorized according to gender and treatment with steroids

	Male	**Female**	**Total**
Steroids given	45	26	71(40%)
Steroids not given	64	43	107(60%)
Total	109(61%)	69 (39%)	178

Table 2 shows the categorization of the patients according to age, mean duration of hospital stay, and associated comorbidities among them. When the patients were distributed according to age majority of them (53%) belonged to the younger age group (18-40 years) in the steroids-administered group of patients. Such a difference in age distribution was not seen in the other group.

The mean duration of hospital stay was slightly higher in the steroids-given group when compared with the group of patients in whom steroids were not given.

When we analyzed the patient's comorbidities like diabetes mellitus, hypertension, Cerebrovascular accidents, coronary artery disease, HIV, liver disease, and malignancy, they were found significantly higher with 82% in the older patients (>60 years) in the steroid-given group.

Table 2: Age distribution of the patients according to age, mean duration of hospital stay, and associated comorbidities.

Demographic details	**18-40 years**	**41-60 years**	**>60 years**	**Total**
Male	43	33	33	109
Female	22	25	22	69
Steroids given	21(30%)	30 (42%)	20 (28%)	71
Steroids notgiven	57 (53%)	35(33%)	15(14%)	107
Mean duration	8	8	9	-

of hospital stay (in days) in steroids not given group of patients				
Mean duration of hospital stay (in days) in the steroids-given group of patients	10	9	9	-
Comorbidities Steroids not given group Steroids given group	 5(10%) 3(18%)	 19(53) 15(71%)	 15(68%) 27(82%)	-

Table 3 shows the steroids not given group who were further categorized as patients under >95 % oxygen saturation on room air, <94 % oxygen saturation on room air, and <89% oxygen saturation on room air at the time of admission. 89% of the patients had Spo2 >95 at the time of admission. When the disease outcome was analyzed two deaths were seen in the patients who presented with <89% oxygen saturation on room air at the time of admission. The mean of the baseline CRP done at the time of admission in this group is also shown in the table.

Table 3: Mean of CRP in the Steroids not given group categorized based on oxygen saturation with the disease outcome

Oxygen saturation	% of patients n=107	Mean of CRP at admission	Disease outcome
>95 on room air	89	17	No deaths
<94 on room air	4	46	No deaths
<89 on room air	7	35	2 deaths

Table 4 depicts the group of patients for whom steroids were given. They are categorized as responders and non-responders based on a 50% reduction in the CRP level after 72 hours when compared with at the time of admission and also based on oxygen saturation levels at the time of admission. 70% of the patients were responders and 30%were non-responders. A significant reduction in the mean of CRP was seen in responders. There was no such significant reduction in the mean of CRP in the non-responders group. 5 deaths were seen among the patients who were admitted with <89% of oxygen saturation.

The Chi-square test of independence and P value was calculated among the responders and non-responders to find the significance between the patient's oxygenation status, mean CRP values during and 72 hours after admission, and patient outcomes. The P value was significant at <0.0435 among the responders and among the non-responders P value was <0.002665.

Table 4: Responders and Non-responders in the Steroids given group with the mean of CRP at the time of admission and after 72 hours of admission

Oxygen saturation	Response to steroids	Mean of CRP at admission	Mean of CRP mean after 72 hours	Deaths
Responders n=49 (30%)				
>95 on room air	24	46	10	0
<94 on room air	17	70	15	0
<89 on room air	8	54	12	0
P value <0.0435				
Non-responders n=22(70%)				
>95 on room air	11	29	28	0
<94 on room	3	49	41	0

air				
<89 on room air	8	43	45	5
P value <0.002665				

The area under the receptor operating curve was 0.911. This shows that CRP has good sensitivity and specificity as a test to monitor the progression of the disease with good predictive value.

Graph 1:

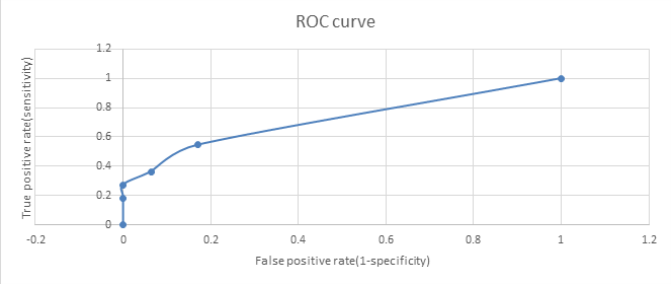

Table 5 shows the odds ratio as a measure of association among the responders and non-responders with the disease outcome(death). The odds ratio was 0.77, (0.37,1.63) at 95 %CI. This proves that CRP responders had a reduced risk of death when compared to non-responders.

Table 5: Unadjusted odds ratio in the steroid-given group of patients with the disease outcome.

n=71	Steroids given	Deaths
Responders	49 (70%)	0
Non-responders	22 (30%)	5

Table -6 shows the vaccination status among the patients in our study. Among the 178 patients, 105(59%) were vaccinated and 73(41%) were not vaccinated. Six deaths were seen in non-vaccinated patients and one death among vaccinated patients

Table6: Vaccination status of patients enrolled in the study

	Vaccinated	Non vaccinated
Total patients n=178	105 (59%)	73 (41%)
Deaths	1	6

Discussion

In our study, 40% of the patients were in the steroid not given group and 60% were in the steroid-given group. The mean duration of hospital stay was 10 days and 8 days in the steroid-given and the not given group respectively. As the patients in the steroid not given group had good oxygen saturation and were comparatively healthier than the patients in the steroids-given group, the mean duration of hospital stay was less. However, the difference was not much significant. A study done by Amidyala Lingaiah and VCS Srinivasa Rao Bandaru et al in Hyderabad found that the mean duration of hospital stay in COVID-19 patients was 10.9 ± 6.0 days[6].

We analyzed the following comorbidities like diabetes mellitus, hypertension, cerebrovascular accidents, coronary artery disease, HIV, liver disease, and malignancy, and found that they were significantly higher with 82% in the older patients and (>60 years) in the steroid-given group.

SARS-CoV-2 utilizes ACE-2 receptors found at the surface of the host cells to get inside the cell. Certain comorbidities are associated with a strong ACE-2 receptor expression and higher release of proprotein convertase that enhances the viral entry into the host cells. These lead the patient into a vicious infectious circle of life and are substantially associated with significant morbidity and mortality[11].

Peter M. Mphekgwana and Musa E. Sono-Setati et al in a study done in South Africa found that

(53%) were hypertensive and 50% of COVID-19 patients were diabetic [7].

In another study done by Mahmoud Sadeghi-Haddad-Zavareh and Masomeh Bay ani et al in COVID-19

patients found that nearly half of the patients had comorbidities, such as diabetes (27.7%), cardiovascular disease (24.9%), and hypertension (22.8%)[8].

In our study, we found that 89% of the patients in the steroid not given group had Spo2 >95 at the time of admission. 2 deaths were seen in patients admitted with oxygen saturation <89%.

Mphekgwana PM, Sono-Setati ME, et al in their study on COVID-19 patients found that mortality with SpO2 levels less than 95% were in greater numbers than those patients with SpO2 levels greater than or equal to 95%[7].

In another study done by Mejía F, Medina C, and Cornejo E, et al, they found that oxygen saturation (SaO_2) values of less than 90% on admission correlated with mortality, presenting 1.86 (95%CI: 1.02–3.39), 4.44 (95%CI: 2.46–8.02) and 7.74 (95%CI: 4.54–13.19) times greater risk of death for SaO_2 of 89–85%, 84–80% and <80%, respectively, when compared to patients with SaO_2 >90%[9]. Hypoxia aggravates inflammatory response due to cytotoxic damage to cells. This aggravated inflammatory response leads to multi-organ failure and death. Hence monitoring Sp02 levels in covid positive patients becomes necessary to prevent such complications. Patients with comorbidities and the elder age group develop hypoxemic damage to tissues much faster.

In our study, we classified 70% of the patients as responders and 30% as non-responders. In a similar study done by Zhu Cui, Zachary Merritt, et al among the 324 patients who received corticosteroids, 131 (40.4%) were classified as responders, 92 (28.4%) were classified as non-responders, and 101 (31.2%) were undetermined[4].

Steroids enter the cytoplasm and act on the nuclear receptors which results in the synthesis of specific mRNA causing protein synthesis which leads to responses. It downregulates the hyperactivation of the components of both innate (neutrophils) and acquired (T and B lymphocytes) immune systems and the cytokine storm that characterizes severe cases of covid-19[11]. As a result, a significant reduction in the inflammatory markers can be seen in these patients which can be measured by certain tests like CRP.

A significant reduction in the mean of CRP was seen in responders. There was no such significant reduction in the mean of CRP in the non-responders group

In our study, there was an increase in the median of CRP in non-responders after 72hrs with the initial median of CRP being 13, whereas a significant reduction of the median of CRP from 54 to 6, was seen in responders. Zhu Cui, Zachary Merritt, et al in their study showed an initial median CRP of 16.3 at the time of admission and a median CRP of 16.5 and 16.6 in responders and non-responders respectively[4]. The Chi-square test of independence and P value was calculated among the responders and non-responders to find the significance between the patient's oxygenation status, mean CRP values during and 72 hours after admission, and patients' outcomes. The P value was significant at <0.0435 among the responders and among the non-responders P value was <0.002665.

Mortality was 10% in non-responders, whereas in responders, no deaths were noted. The P value was significant at <0.00001. Zhu Cui and Zachary Merritt, et al observed inpatient mortality rate was 25.2% among CRP responders and 47.8% among CRP non-responders and p <0.01[4]. Milad Sharif pour and Srikant Ranga Raju et al in their study found that patients who survived had lower peak CRP levels and earlier declines in CRP

levels. CRP levels were significantly higher in patients who died compared to those who survived ($p<0.001$)[9].

In our study, the unadjusted odds ratio as a measure of association among the responders and non-responders with the disease outcome(death) was 0.77, (0.37,1.63) at 95 %CI. CRP responders had a reduced risk of death when compared to non-responders.

This correlated well with the study done by Zhu Cui and Zachary Merritt, et al who found that the odds of inpatient mortality among CRP responders were strongly and significantly reduced compared with those among non-responders in an unadjusted odds ratio [OR], 0.37; 95% CI, 0.21-0.65; P = .001) [4].

Various studies showed that consideration should be given to the early administration of corticosteroids, particularly if inflammatory markers are elevated. This has a significant reduction in the mortality of the patients[12].

The area under the receptor operating curve was 0.911. This shows that CRP has good sensitivity and specificity as a test to monitor the progression of the disease by detecting the reduction in its values to <50% after 72 hours of steroid treatment.

Mejía F and Medina C et al on analysis of the ROC curve in their study illustrated an 0.706 area under the curve (AUC) for CRP levels as a predictor of disease severity (95% CI: 0.649–0.764; $P < 0.001$)[9]. The levels of CRP measured in the blood increase, when there is tissue damage, acting as a marker for an unamplified acute phase response and dysregulated inflammation. Hence, higher CRP levels in the blood are diagnostic of extensive tissue damage and pathological inflammatory response[2].

Conclusion

CRP has a good predictive value for detecting the response to corticosteroid treatment. A high index of suspicion has to be borne in mind among the patients whose CRP levels are not decreasing after 72 hours of steroid administration. In our study, we found that mortality was high in that group of patients.

References

1. Pepys MB. C-reactive protein predicts outcome in COVID-19: Is it also a therapeutic target? Eur Heart J. 2021 Jun 14;42(23):2280-2283.

2. Potempa LA, Rajab IM, Hart PC, Bordon J, Fernandez-Botran R. Insights into the Use of C-Reactive Protein as a Diagnostic Index of Disease Severity in COVID-19 Infections. Am J Trop Med Hyg. 2020 Aug;103(2):561-563. doi: 10.4269/ajtmh.20-0473. Epub 2020 Jun 25. PMID: 32588812; PMCID: PMC7410479.

3. Zhang J, Meng G, Li W, Shi B, Dong H, Su Z, Huang Q, Gao P. Relationship of chest CT score with clinical characteristics of 108 patients hospitalized with COVID-19 in Wuhan, China. Respir Res. 2020 Jul 14;21(1):180. doi: 10.1186/s12931-020-01440-x. PMID: 32664991; PMCID: PMC7359422.Cui Z, Merritt Z, Assa A, et al. Early and Significant Reduction in C-Reactive Protein Levels After Corticosteroid Therapy Is Associated with Reduced Mortality in Patients With COVID-19. J Hosp Med. 2021 Mar;16(3):142-148.

4. 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 May 15;19(1):18. DOI: 10.1186/s12941-020-00362-2. PMID: 32414383; PMCID: PMC7227180.

5. Lingaiah A, Srinivasa Rao Bandaru VCS. Role of Biomarker in COVID-19: A Study from Tertiary Care Center. Ann Infect Dis Epidemiol. 2021; 6(1): 1062.

6. Mphekgwana PM, Sono-Setati ME, Maluleke AF, Matlala SF. Low Oxygen Saturation of COVID-19 in Patient Case Fatalities, Limpopo Province, South Africa. Journal of Respiration. 2022; 2(2):77-86. https://doi.org/10.3390/jor2020006

7. Research Article C-Reactive Protein as a Prognostic Indicator in covid-19 Patients Mahmoud Sadeghi-Haddad-Zavareh, 1 Masomeh Bay ani, 1 Mehran Shokri, 1 Soheil Ebrahim pour, 1 Arefeh Baba Zadeh, 1 Rahele Mehraeen, 2 Emadoddin Moudi, 3 Ali Rostami, 1 Mohammad Barary, 4 Akram Hosseini, 5 Ali Bijani, 6 and Mostafa Javanian

8. Mejía F, Medina C, Cornejo E, Morello E, Vásquez S, Alave J, Schwalb A, Málaga G. Oxygen saturation as a predictor of mortality in hospitalized adult patients with COVID-19 in a public hospital in Lima, Peru. PLoS One. 2020 Dec 28;15(12): e0244171. DOI: 10.1371/journal.pone.0244171. PMID: 33370364; PMCID: PMC7769479.

9. Sharif pour M, Ranga Raju S, Liu M, Alabyad D, Nahab FB, Creel-Bulos CM, Jabaley CS; Emory COVID-19 Quality & Clinical Research Collaborative. C-Reactive protein as a prognostic indicator in hospitalized patients with COVID-19. PLoS One. 2020 Nov 20;15(11): e0242400. DOI: 10.1371/journal.pone.0242400. PMID: 33216774; PMCID: PMC7679150.

10. Thakur M, Datusalia AK, Kumar A. Use of steroids in COVID-19 patients: A meta-analysis. Eur J Pharmacol. 2022 Jan 5; 914:174579. doi: 10.1016/j.ejphar.2021.174579. Epub 2021 Oct 19. PMID: 34678244; PMCID: PMC8525014.

11. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, Abosalif KOA, Ahmed Z, Younas S. COVID-19, and comorbidities: Deleterious impact on infected patients. J Infect Public Health. 2020 Dec;13(12):1833-1839. doi: 10.1016/j.jiph.2020.07.014. Epub 2020 Aug 4. PMID: 32788073; PMCID: PMC7402107.

12. Ho KS, Narasimhan B, Di Fabrizio L, Rogers L, Bose S, Li L, Chen R, Sheehan J, El-Halabi MA, Sarosky K, Wang Z, Eisenberg E, Powell C, Steiger D. Impact of corticosteroids in hospitalized COVID-19 patients. BMJ Open Respir Res. 2021 Apr;8(1): e000766. DOI: 10.1136/bmjresp-2020-000766. PMID: 33811098; PMCID: PMC8023732.