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Evaluation of C-Reactive Protein and High Resolution Computed Tomography Scan Score to Initiate Early Steroid Therapy in Patients with COVID-19 Infection

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ABSTRACT

Background: The severity of COVID pneumonia depends on the degree of lung parenchyma inflammation. This study aimed to identify prognostic factors for COVID-19 and examines the relationship between CRP levels and computed tomography Severity Scores (CTSS).

Methods: An observational study was conducted at Dr. Ziauddin Hospital, Clifton campus, Karachi, Pakistan, from June to November 2021. Purposive sampling enrolled 209 patients, aged 18 years and older, PCR-confirmed cases, requiring both hospitalization and HRCT. Age, sex, admission CRP, symptom duration, disease severity at presentation, CTSS, length of hospital stays, and outcomes (death or discharge) were captured. STATA-12 was used for analysis. Chi-square assessed categorical variables' association with outcomes. Pearson/Spearman-rank test evaluated the correlation between CRP and CTSS. Binary logistic regression identified significant prognostic factors, and linear regression determined the association coefficient between CTSS and CRP (3.00; p=0.00). The coefficient established CRP cutoff for Moderate disease starting >= 27mg/L to initiate steroid therapy.

Results: Disease severity on presentation ($p < 0.001$), HRCT score ($p < 0.001$), hospital stay length ($p = 0.002$), prior illness duration ($p = 0.011$), and elevated CRP levels ($p = 0.012$) were associated with outcomes. A Spearman's rho of 0.336 indicated a positive correlation between HRCT and CRP levels. Logistic regression showed CRP (OR=1.0051, p=0.003) and CT-severity-score (OR=2.1155, p=0.002) as significant. Linear regression yielded a coefficient of 3.0094 ($p < 0.001$) for CTSS and CRP levels. The transition from mild to moderate disease occurred at a CRP level of establishing ≥27 mg/L.

Conclusion: A CRP cutoff of 27 mg/L can guide early steroid therapy to prevent disease progression and monitor therapeutic response.

Keywords: COVID-19 Infection, CRP, Severity Score.

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INTRODUCTION

The COVID-19 pandemic caused severe mortality and morbidity worldwide. The clinical presentation of COVID-19 includes fever (98%), cough (76%), dyspnea (55%), myalgia or weakness (44%), sore throat (29%), headache (8%), hemoptysis (5%), and loose stools (3%) and with various neurological symptoms[1]. Many biochemical markers are believed to be predictive for disease severity and progression. C-reactive protein (CRP) is a strong acute-phase reactant protein involved in the pro-inflammatory cycle by activating cytokines in the body[2]. A cytokine storm is a severe immune-pathological feature of COVID-19 infection. The virus rapidly multiplies in the endothelium, with mass production of pro-inflammatory chemokines and cytokines. potentially leading to acute respiratory distress syndrome (ARDS) and multiple organ failure[3].

Initially, RT-PCR was the most common diagnostic tool for confirming COVID-19 infection[4]. Acute respiratory distress is the most common form of lung injury in COVID-19 infections, typically presenting in 30% of cases[5]. High-resolution chest computed tomography (HRCT) plays a key role in evaluating the extent of lung injury, often detecting abnormalities even in asymptomatic patients. Studies have shown that the sensitivity of HRCT in diagnosing COVID-19 pneumonia ranges from 75-97%, although its specificity is only 25%[6]. Common HRCT findings include ground-glass opacity and lung consolidation, with lesions often peripherally and basally located[7].

It has been noticed that the higher the CRP elevation in COVID-19 infection, the greater the lung involvement and the higher the oxygen demand. Establishing an association between CRP levels and HRCT scores in COVID-19 could help categorize disease severity and predict worsening based on CRP alone. To the best of our knowledge, no study has been conducted in our population to measure the association between CRP levels and HRCT disease scores.

The purpose of this study was to identify prognostic factors and evaluate the correlation between CRP levels and CTSS. If a correlation is found, the next step is to determine the CRP cutoff level that predicts the appearance of infiltrates on HRCT. If an association is proven, CRP values can be used as a surrogate marker for CT severity, allowing for the early initiation of steroid therapy in the course of the disease .

METHODS

An observational study was carried out at Dr. Ziauddin Hospital, Clifton Campus, Karachi, after approval from the ethical approval committee under the Ref:4650122NIMED. The study population is all those patients age 18 years or above diagnosed case of COVID pneumonia on basis of COVID PCR with radiological findings on HRCT compatible with COVID-19 Infection who are PCR confirmed cases of COVID-19 infection and have CT proven infiltrates involving the lung parenchyma during a period of 6 Months from June 2021 to Nov 2021. Baseline data were collected from medical records and included age, sex, CRP level at presentation, duration of presenting symptoms, length of hospital stay, COVID-19 PCR status, CT severity score, disease category at presentation, and outcome (death or discharge).

The diagnostic criteria for COVID-19 are multifaceted and based on clinical symptoms, laboratory confirmation, disease severity, and radiological findings[4]. Clinically, patients suspected of having COVID-19 typically present with symptoms such as fever, cough, dyspnea, and loss or alteration of the sense of taste or smell. Laboratory confirmation is primarily achieved through a positive reverse transcription polymerase chain reaction (RT-PCR) test, which remains the gold standard for diagnosing SARS-CoV-2 infection[4]. Disease severity is classified following the criteria proposed[13] where mild cases are characterized by minor clinical symptoms without evidence of pneumonia on lung CT scans. Moderate cases present with fever and cough, accompanied by radiological signs of pneumonia. Severe cases involve respiratory distress, defined by a respiratory rate exceeding 30 breaths per minute, resting oxygen saturation (O_2Sat) at or below 93%, and/or a PaO_2/FiO_2 ratio of 300 mmHg or less. Radiological assessment plays a crucial role in both the diagnosis and evaluation of disease progression. Chest CT scans often reveal bilateral, peripheral airspace opacities—commonly in the form of ground-glass opacities—most prominently in the lower lung zones. The CT Severity Score (CTSS), derived from high-resolution CT (HRCT)

images, quantifies lung involvement by evaluating 20 defined lung regions (from 18 anatomical segments) and assigning scores from 0 to 2 based on the degree of parenchymal involvement. The cumulative score ranges from 0 to 40. CT evaluations are independently conducted by a senior radiologist with over a decade of experience, who remains blinded to the clinical diagnosis to ensure unbiased assessment. This comprehensive diagnostic framework facilitates the accurate identification and categorization of COVID-19 cases[13].

The grading of the CT Severity Score (CTSS) is essential for categorizing the extent of pulmonary involvement in COVID-19 patients. According to the established criteria, a CTSS of ≤8 indicates mild disease, a score between 9 and 15 signifies moderate disease, and a score of ≥16 is indicative of severe disease[13]. All thin-section CT images were meticulously evaluated using window width and level settings of 1000 to 2000 Hounsfield Units (HU) and -700 to -500 HU, respectively, to accurately assess the lung parenchyma. High-resolution CT (HRCT) scans were performed using a 16-detector CT scanner (Emotion; Siemens). During the imaging procedure, patients were placed in a supine position, and scans were obtained during a single inspiratory breath-hold, encompassing the entire lung field from apex to costophrenic angle. The CT scan parameters included an X-ray tube voltage of 120 kVp, tube current of 350 mAs, a rotation time of 0.5 seconds, pitch of 1.0, section thickness and intersection space both set at 5 mm, with additional image reconstruction performed using a sharp convolution kernel to generate slices with a thickness of 1.5 mm. All images were managed and reviewed using the standard clinical picture archiving system, Clear Canvas. For the study, the sample size was calculated using the "Correlation Sample Size Calculator", with an alpha level of 0.05, statistical power of 80%, and a minimum expected correlation coefficient of 0.2, chosen conservatively to avoid missing weaker associations. Based on these parameters, the required sample size was determined to be 194. To account for a potential 10% attrition rate, the final sample size was increased to 214 participants[10,11,22].

For statistical analysis, continuous variables were summarized using either mean and standard deviation, depending on their distribution. Categorical variables were presented as frequencies and displayed in tabular form. Association between categorical variables and the outcome variable was assessed using the Chi-square test. The correlation between CRP and CT severity scores (CTSS) was evaluated using either the Pearson or Spearman rank tests, depending on the distribution as assessed by the Shapiro-Wilk test. If either variable was not normally distributed, the Spearman rank test was employed. Binary logistic regression was utilized to identify significant prognostic factors and calculate Odds Ratios. Linear regression determined the coefficient of association between CT severity score and CRP value. This coefficient was used to derive CRP thresholds for disease categories (mild, moderate, and severe) based on CT scoring. A two-sided p-value of <0.05 was considered statistically significant. All analyses were conducted using STATA version 12.

RESULTS

Table 1a: Summary of Continuous Variables

Continuous Variable	Mean	Std. Deviation	Minimum	Maximum
Age (years)	60.2	14.88	8	91
C-Reactive Protein (CRP) (mg/L)	143.46	99.27	0.5	542
Duration of Symptoms (days)	7.8	4.4	1	22
Length of Hospital Stay (days)	9.44	8.70	1	75
CT Severity Score (CTSS)	23.27	8.59	0	38

This table summarizes the characteristics of both continuous and categorical variables of the study population with mean, standard deviations, minimum and maximum values for continuous and proportions for categorical variables, respectively. This data provides insights into patient demographics, disease severity, and clinical outcomes. **Table 1a** summarizes patient data, with an average age of 60.2 years and CRP levels of 143.46 mg/L. Symptoms lasted an average of 7.8 days, and the mean hospital stay was 9.44 days. The average CT severity score was 23.27. Most patients were male (73.2%), and 70.8% were discharged, while 29.2% died. Disease severity was mostly "Severe" (59.3%), with a smaller proportion in "Mild" (14.4%) and "Moderate" (15.8%). Most patients had a hospital stay of 1-10 days (70.8%), and 42% had symptoms lasting 6-10 days.

Table 1b: Summary of Categorical Variables

Categorical Variables	Frequency (%)
Gender	
Male	153 (73.2%)
Female	56 (26.8%)
Outcome	
Discharge	148 (70.8%)
Death	61 (29.2%)
Clinical Disease Category	
Mild	30 (14.4%)
Moderate	33 (15.8%)
Severe	124 (59.3%)
Critical	22 (10.5%)
CT Severity Score Category	
Mild (0–8)	18 (8.5%)
Moderate (9–15)	20 (9.4%)
Severe (≥16)	171 (81.7%)
Length of Hospital Stay (categorized)	
1–10 days	148 (70.8%)
11–20 days	38 (18.2%)
21–30 days	19 (9.1%)
≥31 days	4 (1.9%)
Duration of Illness (categorized)	
1–5 days	67 (32.0%)
6–10 days	88 (42.0%)
11–15 days	48 (23.0%)
16–20 days	4 (1.9%)

The **Table 1b** presents a descriptive analysis of patient outcomes (discharge or death) based on variables such as sex, clinical disease category, CT severity score, length of hospital stays, and duration of illness. There was no significant difference in outcomes based on sex ($p = 0.96$). A significant association was found between disease severity and outcomes ($p = 0.002$), with more deaths in the "Severe" category. CT severity score showed no significant relationship with outcomes ($p = 0.206$). Length of hospital stay significantly influenced outcomes ($p = 0.002$), with shorter stays resulting in more discharges. Duration of illness also showed a significant association ($p = 0.011$), with patients experiencing 6-10 days of symptoms having more deaths.

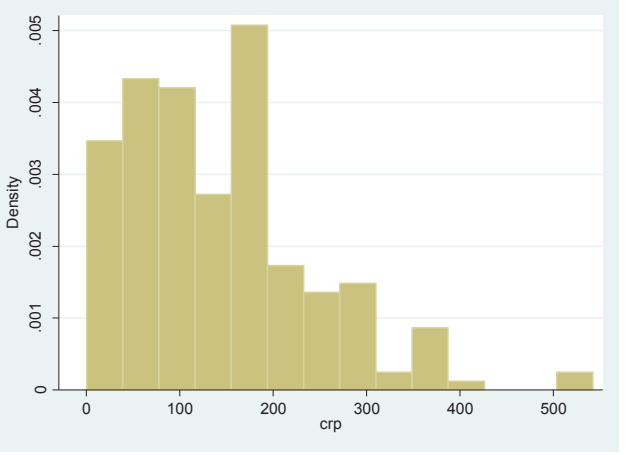
Table 2: Descriptive Analysis of Investigatory Parameters

Study Variable	Discharge (n)	Death (n)	p-value
Sex			
Male	106	45	0.96
Female	40	16	
Clinical Disease Category			
Mild	27	3	**0.002**
Moderate	28	5	
Severe	93	53	
Critical	–	–	
CT Severity Score Category			
0–8	18	3	0.206
9–15	16	4	
16–40	117	54	

Length of Hospital Stay (Categorized)			
1–10 Days	114	34	**0.002**
11–20 Days	18	20	
21–30 Days	12	7	
>30 Days	4	0	
Duration of Illness (Categorized)			
1–5 Days	43	24	**0.011**
6–10 Days	60	28	
11–15 Days	42	6	
16–20 Days	3	1	
>20 Days	0	2	

Table 2 compares the individual study variables with the outcome measure of death or discharge with p<0.05 taken as significant.

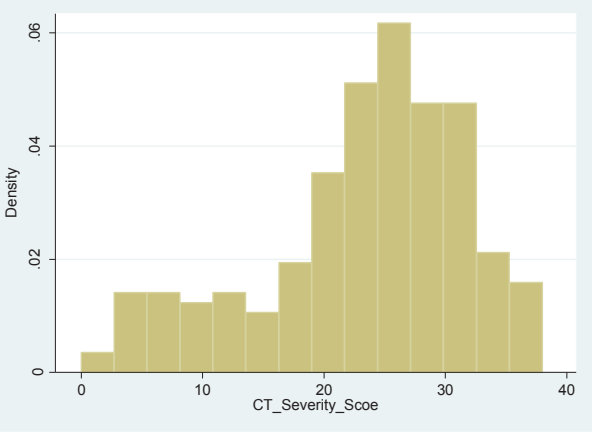
The Shapiro-Wilk test for CRP (C-Reactive Protein) was conducted to assess the normality of the data distribution. The test yielded a W statistic of 0.938 with a p-value of 0.0, indicating that the CRP values are not normally distributed. This suggests that the distribution of CRP does not follow a normal distribution, and non-parametric methods may be more appropriate for subsequent analyses **(Figure 1)**.



Shapiro-Wilk test for CRP, W statistic 0.938, p0.0, Not normally distributed.

Figure 1: The Shapiro-Wilk test for CRP

The Shapiro-Wilk test for the CT Severity Score (CTSS) was performed to examine the normality of the data distribution. The test resulted in a W statistic of 0.945 with a p-value of 0.0, indicating that the CTSS values are **not normally distributed**. This suggests that the distribution of CTSS does not follow a normal distribution, and non-parametric methods may be more suitable for further analysis **(Figure 2)**.



Shapiro Wilk test for CTSS, W statistic 0.945, p0.0; Not normally distributed

Figure 2: The Shapiro-Wilk test for CTSS

The correlation between CRP (C-Reactive Protein) and CTSS (CT Severity Score) was assessed using Spearman's Rank Correlation Coefficient. The result showed a Spearman's Rho of 0.3366, indicating a moderate positive correlation between the two variables. The p-value was less than 0.01, confirming that this correlation is statistically significant. This suggests that higher CRP levels are moderately associated with higher CT severity scores.

Spearman's Rho – 0.3366 – (Positive correlation), p0.0 [12] .

Spearman ρ	Correlation
≥0.70	Very strong relationship
0.40-0.69	Strong relationship
0.30-0.39	Moderate relationship
0.20-0.29	Weak relationship
0.01-0.19	No or negligible relationship

Table 3: Binary Logistic Regression of Factors Associated with Patient Mortality

Variable	Category	Coefficient (β)	Standard Error (SE)	Odds Ratio (OR)	p-value	95% CI for OR
Sex		-0.241	0.452	1.226	0.595	–
Age (years)	>17	0.0365	0.0153	1.0372	0.017	1.0064 – 1.0665
CRP (mg/L)	>=1	0.0051	0.0019	1.0051	0.007	1.0013 – 1.0088
Duration of Illness (days)	>=1	-0.0547	0.0464	0.9467	0.239	–
CT Severity Score	0-40	0.0971	0.0285	1.1020	0.001	1.0411 – 1.1531
Length of Hospital Stay (days)		-0.0175	0.0236	0.9825	0.457	–
	Moderate	-0.1541	–	0.8571	0.854	–
	Severe	0.4219	–	1.5249	0.540	–
	Critical	3.505	–	33.3007	0.001	1.6266 – 5.3845

The **table 3** highlights the significant variables influencing patient outcomes, identifying age, C-reactive protein (CRP) levels, and the CT Severity Score as key predictors of a worse prognosis in COVID-19 cases. Among these, CRP and CT Severity Score demonstrated a strong correlation. To further explore this relationship, a linear regression analysis was conducted between CT Severity Score and CRP levels. The results of the model revealed a regression coefficient of 3.0094, with a highly significant p-value of less 0.001, indicating a robust statistical association. The 95% confidence interval for the coefficient ranged from 1.481 to 4.537, confirming that higher CRP levels are significantly associated with increased CT Severity Scores, and consequently, with more severe lung involvement in COVID-19 patients.

Figure 3 evaluates the normality of the residuals derived from the linear regression model. A well-distributed and approximately linear pattern in the plot suggests that the residuals adhere to a normal distribution, which is a key assumption for the validity of linear regression. When this condition is met, it strengthens the reliability of the model's estimates and supports the appropriateness of using linear regression to assess the relationship between CT Severity Score and CRP levels.

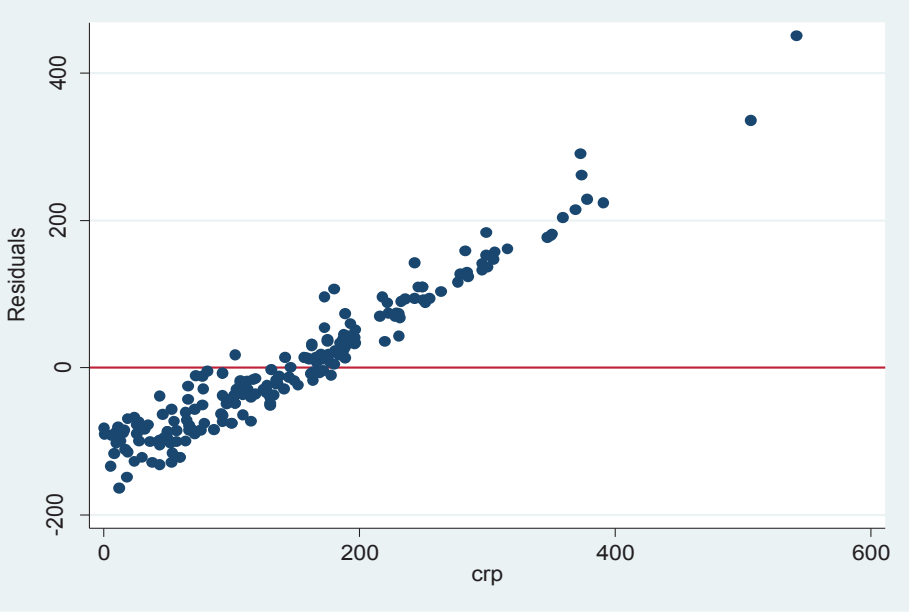


Figure 3: Residual with predicted CTSS

The White test was employed to assess homoscedasticity, which refers to the assumption of constant variance in the residuals of a regression model. The test produced a value of 4.77 with a corresponding p value of 0.092. Since this p-value exceeds the commonly used significance level of 0.05, there is no statistically significant evidence of heteroscedasticity. This indicates that the variance of the residuals remains reasonably consistent across the range of predicted values, thereby supporting the assumption of homoscedasticity and reinforcing the validity of the regression model **(Figure 4)**.

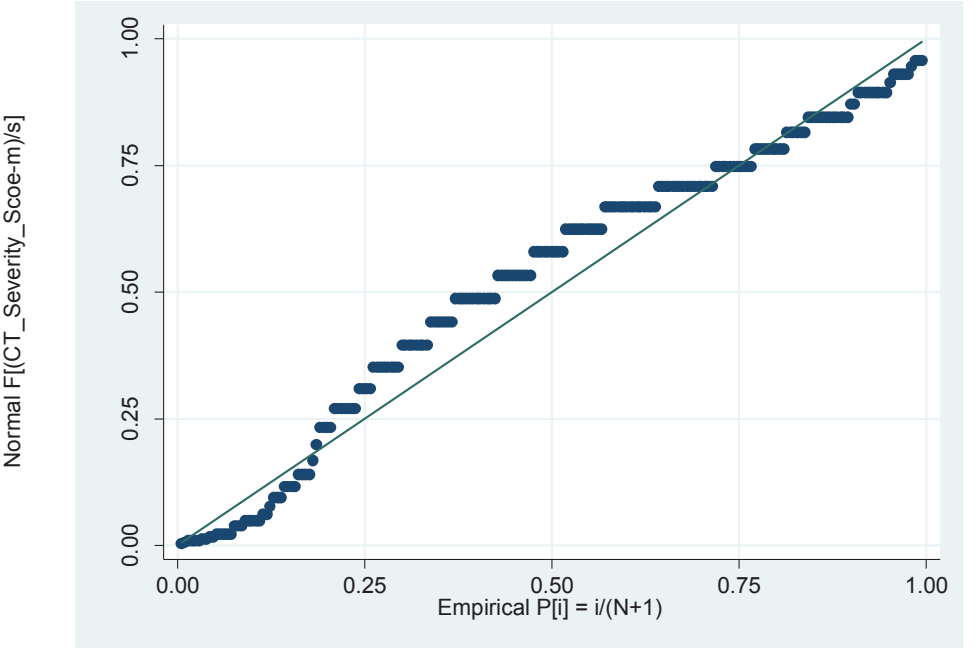


Figure 4: CT - SS Normality Probability Plot

These figures collectively demonstrate a significant relationship between CT severity and CRP levels, confirming the model's reliability with no major violations of regression assumptions.

Table 4 :Using Linear Regression to Calculate the CRP Value for CT-SS Grades using CRP Co-efficient (3.00)

CT Severity Score	Significance	Corresponding Minimum CRP Value
=< 8	Mild	<24mg/L
9 – 15	Moderate	27-45mg/L
>=16	Severe	>=48mg/L

Table 4 shows the relationship between CT Severity Scores and CRP levels. For mild disease (CTSS ≤8), CRP is typically under 24 mg/L. Moderate disease (CTSS 9-15) corresponds to CRP levels between 27-45 mg/L, while severe disease (CTSS ≥16) is associated with CRP levels ≥48 mg/L. This highlights the correlation between lung severity on CT and inflammatory response as indicated by CRP.

DISCUSSION

The results revealed a significant correlation between CRP values and HRCT severity scores, suggesting that CRP may serve as a biomarker for assessing disease severity and progression as evidenced by HRCT. Lung imaging is considered an essential component of the diagnostic workup in COVID-19 patients[14].

In our study, the mean age of COVID-19 patients was in the middle-aged group, which exhibited higher disease severity and mortality rates. This aligns with recent findings that also indicate a male predominance in COVID-19 infections[15]. Severe disease patterns have been more frequently observed in males, possibly due to the protective effects of estrogen in females[16]. The severity of the disease is influenced by multiple factors, including patient comorbidities, lack of proper education, poor living conditions, delayed healthcare access, and existing healthcare infrastructure[17]. Literature indicates that risk factors such as hypertension, diabetes, lung, and coronary artery diseases are associated with poor prognosis, particularly when multiple risk factors are present [18,19].

Our findings also showed that serum CRP levels significantly correlated with CT severity scores, which aligns with the activation of the host immune response and can be considered as a predictive marker for likelihood of disease progression[20]. CT imaging assesses the extent and severity of pulmonary involvement in COVID-19 by visualizing features such as ground-glass opacities, consolidation, and peripheral lesion distribution. Quantifying these using a scoring system makes CT a valuable tool for evaluating disease severity and monitoring progression.

The significant correlation between CRP levels and HRCT severity scores suggests that CRP provides valuable prognostic information. The death rate in our cohort was significantly higher among patients with severe CT findings[21,22]. Monitoring CRP levels alongside HRCT findings may help identify patients at higher risk of disease progression and adverse outcomes, it can be used to stratify disease severity and initiate early steroid therapy, it can also guide steroid dosing; if an inadequate response is observed with the standard Dexamethasone 6 mg dose within 48 hours, then dose can be increased to 12 mg or further to 18 mg to achieve the desired response, indicated by a reduction in CRP levels.

While this study provided valuable insights, there are several limitations. It was a single-center study, exclusion of OPD COVID-19 infections, and only includes those patients who underwent both CRP level testing and chest CT scans, limiting generalizability. CTSS was done using a subjective scoring system, although each scan was independently reported by two experienced radiologists who concurred. Other inflammatory biomarkers and clinical parameters should be evaluated alongside CRP to develop comprehensive prognostic models. Validation studies recommended.

CONCLUSION

In conclusion, the study highlights the association between CRP levels and HRCT severity scores in COVID-19 patients, underscoring the potential utility of CRP as a biomarker for disease severity and progression. Using CRP when in the moderate disease range to start steroids will likely prevent disease progression. CRP value can also be considered as marker for treatment response for steroid dose escalation. Further research is needed to validate these findings and explore the prognostic significance of CRP in larger, prospective cohorts.

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CONFLICT OF INTEREST
None

FUNDING
None

ETHICAL APPROVAL
The study received ethical approval from the Ethical Review Committee of Ziauddin University, under reference number (4650122NIMED).

AUTHORS' CONTRIBUTIONS
NI was responsible for overseeing the ethical review of the study proposal, as well as being involved in the study methodology, implementation, design, data collection, data analysis, and manuscript writing. **MORK** contributed to the conception of the study idea, study design, methodology, statistical analysis, and the writing of the paper. **AHO** was involved in the study design, methodology, statistical analysis, and the review of the paper. **GH** reviewed all HRCT images, provided scoring based on the **CT** pattern, and reviewed the manuscript, particularly in relation to radiological details. Lastly, **SAF** was involved in data collection and the writing of the manuscript.

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