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C-REACTIVE PROTEIN LEVELS AS PREDICTORS OF COVID-19 SEVERITY: A RETROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Since its emergence in China in December 2019, SARS-CoV-2 has posed significant global health challenges due to its rapid spread and high mortality. Predicting COVID-19 severity remains difficult, with some suggesting C-reactive protein (CRP) as a potential early marker for severe cases. This study examines the relationship between CRP levels and COVID-19 severity to better manage the disease and aimed to investigate CRP's utility in prognosticating COVID-19 to improve patient outcomes The study has included patients of more than 18 years diagnosed with COVID-19 infection by RT-PCR method and admitted in either ward or ICU or having any comorbid conditions eg: Diabetes, Hypertension.

Materials and Methods: Analysis regarding serum CRP with the severity of disease was done. Among all statistical tests, Chi-square tests were used where P <0.05 was taken as significant. This two-month retrospective study at Great Eastern Medical School and Hospital, Andhra Pradesh, analyzed data from 152 COVID-19 patients confirmed by RT-PCR. Data on demographics, clinical histories, and CRP levels determined by nephelometry were extracted from the hospital's Laboratory Information System, following ethical approval.

Results: Analysis of 152 COVID-19 patients showed those with CRP levels >100 mg/L had a higher likelihood of severe disease. The values were categorised based on the values we received after the investigation. And the patients were suffering from more severe conditions who had >100mg/L of CRP values. The severity was determined based on the symptoms and signs patients presented during their stay in hospital. The majority (76.3%) had non-severe cases, with a significant 23.7% presenting with severe symptoms. CRP values ranged, with most patients having levels between 8.01-50.0mg/L or <8mg/L, correlating to illness severity.

Conclusion: High CRP levels may serve as an early indicator of potential disease severity in COVID-19, aiding timely intervention. While limited by sample size and being a single-center retrospective analysis, these findings call for larger, multicenter studies with repeated CRP measures for validation. Monitoring high-CRP patients closely is recommended.

Keywords: COVID-19, Prognostic marker, Inflammatory response, Disease severity, Disease progression, Serum marker

INTRODUCTION

COVID-19, a severe acute respiratory syndrome coronavirus, was first identified in Wuhan city, China, in December 2019. The COVID-19 pandemic then being transmitted by air borne route spread quickly around the world [1, 2]. The rapid global spread of SARS-CoV-2, along with the associated high mortality rate, has become a significant global health concern. For those infected by SARS-CoV-2, some of the patients who were categorised in non-severe group did not show hypoxemia or respiratory stress, during COVID-19, indicating a multifaceted disease of SARS-CoV-2 infection. Therefore, panel of biomarkers are required to assess the severity of the disease, among them testing for CRP can be considered as one reliable and convenient biomarker to predict the severity of COVID-19 pneumonia [3]. Clinical studies demonstrated that altered levels of some blood markers might be linked with the degree of severity and mortality of patients with COVID-19 [4, 5, 6, 7, 8]. Of these clinical parameter, serum C-reactive protein (CRP) has been found as a potential marker that changes significantly in severe patient [6].

We hypothesize that CRP can be utilized in predicting the severity of COVID-19 pneumonia based on the symptoms, signs lung CT, Oxygen requirement and treatment protocol . Hence, this study aims to determine the significance of CRP levels in correlation with predicting disease severity in early-stage COVID-19 patients.

MATERIAL AND METHODS

The present study was a hospital based retrospective study conducted for two months, in the Department of Microbiology; Great Eastern Medical School and Hospital, Ragolu, Srikakulam, in Andhra Pradesh. Data was collected for a period of 2 months from April 2021 to May 2021 and was analysed. The study was done abiding all the ethical norms of the Institute and was approved by the institutional ethical committee bearing number 13/IEC/GEMS&H/2020.

Inclusion criteria. Patients with age more than 18 years diagnosed with COVID-19 infection by RT-PCR method and admitted in either ward or ICU or having any comorbid conditions eg: Diabetes, Hypertension during that period were included.

Exclusion criteria. Patients diagnosed with malignancies, solid tumours or any chronic inflammatory diseases or taking immunosuppressive drugs or with recent history of organ transplant were not included in the study as their immunosuppressive state can alter the severity status.

Data collection. All the data regarding the biochemical parameters were extracted from the Laboratory Information System (LIS) of the Institute after taking the permission from the authority. Relevant demographic, previous medication and clinical history of the patient were collected from hospital database.

Sample size calculation. The population was around 230 (since during the study period approximately 230 on an average of COVID-19 patients were admitted daily) So, with 5% marginal errors and 95% Confidence Interval (CI), the sample size was calculated using online sample size calculator and it came around 145. Therefore, total of 152 eligible patients who fulfilled inclusion-exclusion criteria; during the defined period diagnosed for COVID-19 disease confirmed by RT-PCR method were included in the study.

Statistical analysis. Microsoft excel free version were used for statistical analysis. Mean and Standard Deviation (SD) was used to represent continuous variables whereas percentage used for categorical variables. Analysis serum CRP with the severity of disease was done. Among all statistical tests, Chi-square tests were used where $P < 0.05$ was taken as significant.

Among them 116 (76.3%) patients were included from COVID ward, and 36 (23.7%) patients were from various ICUs (Fig. 1).

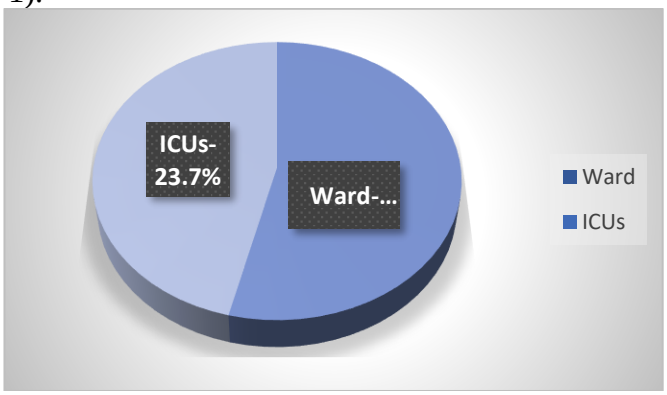

Fig. 1. Distribution of patients from wards and ICUs.

Classification based on severity. World Health Organization (WHO) classifies COVID-19 based on across a wider spectrum, from asymptomatic infection, mild, moderate, severe. The severity categorisation varies from hospital to hospital and the classification may not align with international standards or be consistent across different institutions. As per our hospital policy based on the symptoms, lung CT, Oxygen requirement and treatment protocol, patients were classified in two groups as nonsevere and severe.

Patients who were presented to the hospital without any symptoms as contacts or with mild symptoms or patients who required less than 5 litre/min oxygen or lung CT without pneumonia and without any co-morbidity were kept in COVID ward and categorised as nonsevere patients. patients who presented with symptoms and respiratory distress where respiratory rate is more than 30/min and oxygen saturation is less than 93% with oxygen requirement was more than 5 litre/min and lung CT showing pneumonia and patients who required invasive or non-invasive respiratory assistance were kept in ICU and this group was considered as severe group.

CRP examination. The CRP test was conducted in the hospital central laboratory using Turbidimetric inhibition immune assay. The reagent was C-reactive protein test kit, the normal range of CRP value was up to 6 mg/L.

RESULTS

Data of 152 COVID patients were analysed in this study. Among them 103 (67.7%) were male patients and 49 (32.3%) were females (Fig. 2).

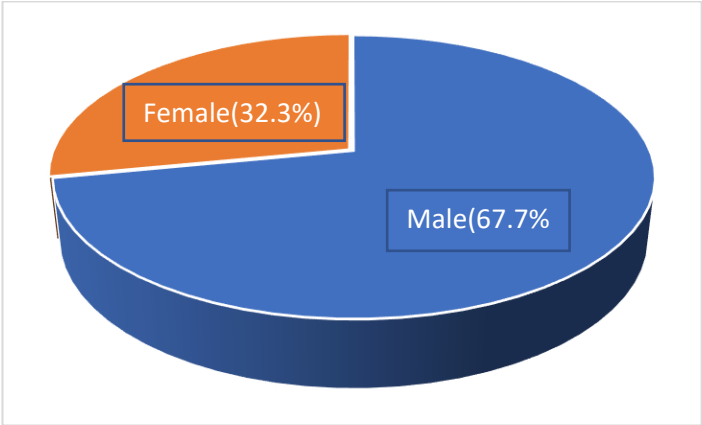

Fig. 2. Gender wise distribution of COVID-19 patients

Distribution of study participants according to the age varied from 18 to 76years, the study showed 73(48.0%) of the patients falls in the age group of 26-50 years and 70(46.1%) of them belong to 51-75 age group (Table 1). Mean Age of study population: 49.5 ± 13.6 years.

Table 1. Age and gender wise distribution of COVID-19 patients

Age	Male (N/%)	Female (N/%)	N/%
18-25	5 (4.9%)	1 (2.0%)	6 (3.9%)
26-50	51 (49.5%)	22 (44.9%)	73 (48.0%)
51-75	45 (43.7%)	25 (51.1%)	70 (46.1%)
>76	2 (1.9%)	1 (2.0%)	3 (2.0%)
Total	103 (100%)	49 (100%)	152 (100%)

116 (76.3%) who were admitted in wards with mild clinical symptoms, categorised in non-severe group. 36 (23.7%) from various ICUs were added in severe group based on their symptoms. Out of 152 patients, 6 (3.94%) of the critically ill patients were succumbed to COVID-19 due to the disease severity and rest 146 (96.06%) were survived (Fig. 3).

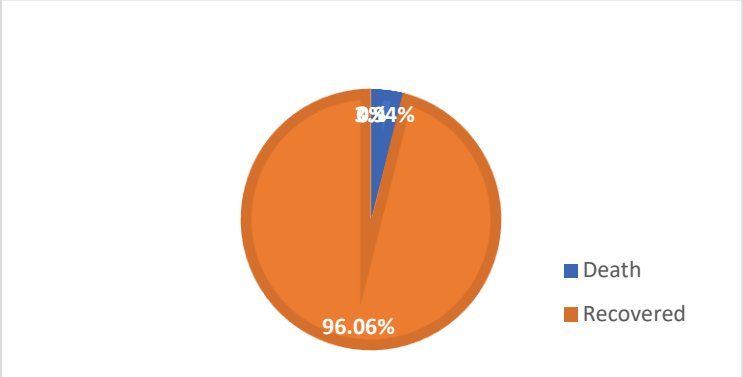

Fig. 3. Distribution of patients according to survival

34.86 % patients had CRP value in 8.01-50.0mg/ L followed by 31.57% who showed < 8mg/L**.** In the severe group**,** 44.44% had >100 mg/L of CRP value (Table 2).

Table. 2. Distribution of COVID-19 patients according to CRP values (mg/L)

CRP Value	Total number (%)	Non-severe no. (%)	Severe no. (%)
0-8.00	48 (31.57%)	48 (41.37%)	0 (0.0%)
8.01-50.00	53 (34.86%)	45 (38.79%)	8 (22.23%)
50.01-100.00	27 (17.7%)	15 (12.93%)	12 (33.33%)
>100	24 (15.78%)	8 (6.89%)	16 (44.44%)
Total	**152 (100%)**	**116 (100%)**	**36 (100%)**

Based on the CRP values and severity status, the mean value of CRP was 85.0 ± 41.1 for severe group and 31.1 ± 38.9 was found to be for nonsevere group. *P*-value (< 0.001) was found to be statistically significant (Table 3).

Table 3. Association of CRP value with severity status.

Variable	Severe	Non-Severe	*P*-value
CRP	^85.0 ± 41.1	^31.1 ± 38.9	#t= 7.158 p < 0.001

^ = Mean ± SD, # =Independent sample t test, Value of p < 0.05 is significant.

Among 152 patients, 27.2 % of males and 16.3 % of females were categorised in severe group, and the result is not statistically significant (*P* = 0.1411) (Table 4).

Table 4. Association between gender and disease severity

S. No.	Variable	Severe	Non-Severe	Total	*P*-value
1	Male	28 (27.2 %)	75 (72.8 %)	103(100%)	P = 0.1411
2	Female	8 (16.3 %)	41 (83.7 %)	49(100%)	
	Total	46	116	152(100%)	

Overall, the most common initial symptoms were fever (67.1 %) and dry cough (51.9 %) followed by fatigue, nausea and chest pain (Table 5).

Table 5. Clinical presentation of COVID-19 patients

Clinical symptoms	Cases (N/%)
Fever	102 (67.1%)
Fatigue	67 (44.1%)
Headache	23 (15.1%)
Dry cough	79 (51.9%)
Expectoration	13 (8.6%)
Chest pain	45 (29.6%)
Nausea	49 (32.2%)
Diarrhea/ Constipation	31 (20.3%)
Loss of smell and taste	59 (38.8%)

Among 152 participants, 12 (7.89%) were diabetic and 8 (5.26%) were hypertensive. 122(80.27%) were not having any comorbid conditions (Fig 4).

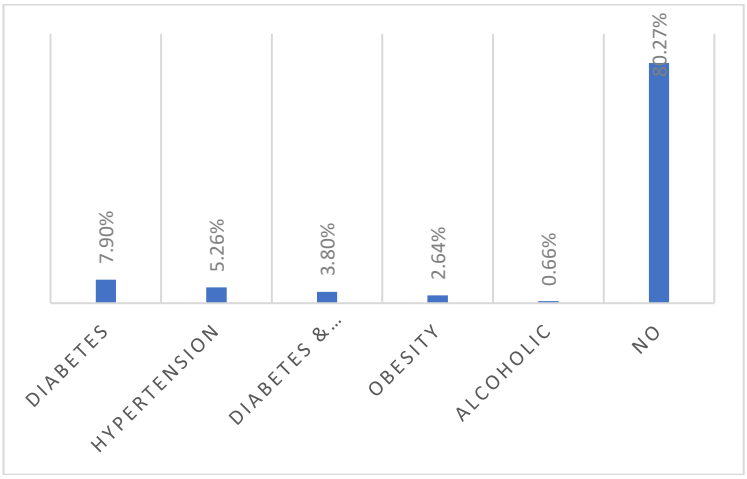

Fig. 4. Distribution of COVID-19 patients with comorbid conditions

Patients who had co-morbid conditions were found to have more severe disease and this association is statistically significant (*P* =0.005) (Table 6).

Table 6. Association of comorbid condition and disease severity

Comorbid conditions	Severity			*P*-value
	No	Yes	Total	
No	99 81.1 %	23 18.9 %	122 100.0 %	*P* =0.005
Yes	17 56.7 %	13 43.3 %	30 100.0 %	
Total	116 76.3 %	36 23.7 %	152 100.0 %	

DISCUSSION

CRP is a cytokine induced acute phase protein that increases in concentration as a result of inflammation. CRP levels in the body is used as a marker of infections and inflammation. In the present observational study, the prognostic value of the CRP in the progression of COVID-19 cases has been assessed. Furthermore, the clinical characteristics of severe COVID-19 patients were compared with those of non-severe patients and analyzed the possible factors associated with disease progression and severity.

In our study, 103 (67.7%) were male patients and 49 (32.3%) were females, which is similar to study done by George M. Bwire *et al.*, several factors including sex hormones and high expression of coronavirus receptors (ACE 2) in men and lifestyle, such as smoking ,drinking among men is high as compared to women [10]. Organism which expresses ACE 2 protein in high number has a facilitated environment for establishing infection by coronavirus. With this correlation between ACE 2 and coronavirus, many studies have quantified the expression of ACE 2 proteins in human cells based on gender ethnicity, as in studying the expression level and pattern of human ACE 2 using a single-cell RNA-sequencing (RNA-seq), analysis indicated that Asian males had higher expression of ACE 2 than female [11].

In our study maximum number of the patients falls in the age group of 26-50 years, where as in other study Most of the patients in this cohort were >40 years old, which was in accordance with the study done by Kenneth I et al., and Guoxin Huang, *et al.*, where average age of the patients was 44.5 years old, Reason might be that older age give rise to more severe inflammatory response, and increased rate of developing into severe and critical types [3, 9].

Current study evaluated the association between CRP and COVID-19 infection, 34.86 % patients had CRP value in 8.01-50.0mg/ L followed by 31.57% who showed < 8mg/L**.** In the severe group**,** 44.44% had >100 mg/L of CRP value, confirmed CRP as a valuable predictor of COVID-19 progression and severity. CRP is a type of protein secreted by liver indicates as an early marker of infection and inflammation [12]. In blood, CRP is less than 10 mg/L; however, rises rapidly within 6 to 8 hours and reach highest in 48 hours from onset of disease [13]. CRP binds to phosphocholine expressed present on the surface of damaged cells [14]. In our study, based on the CRP values and severity status, the mean value of CRP was 85.0 ± 41.1 for severe group and 31.1 ± 38.9 was found to be for nonsevere group. *P*-value (< 0.001) was found to be statistically significant which was in accordance with the study conducted by Mo P, Xing Y, Xiao Y, *et al.* which showed , the mean concentration of CRP was significantly higher in severe patient (46 mg/L) than non-severe patients (23 mg/L)[15] . Yang X, *et al.* study showed the patients having complications such as shock, ARDS, acute kidney injury, and acute cardiac injury have 10-fold higher levels of CRP than the recovered patients which indicates that increased levels of CRP is directly linked to lung injury and have worse prognosis thus plays as a suitable marker in assessing a patient's conditions together with other clinical findings [16].

In our study, 12(7.89%) were diabetic and 8(5.26%) were hypertensive, which is in accordance with study done by Yang X, *et al.* which reported independent role of diabetes on mortality in COVID-19 patients [17]. Diabetes increased viral uptake and higher basal level of pro-inflammatory cytokines present in patients with diabetes, resulting in "cytokine storm" in response to the virus [18].

Our findings suggest a correlation between CRP levels and the severity of COVID-19. Particularly, higher CRP values were observed more frequently among patients in the severe group, suggesting a potential role of CRP as a biomarker for disease progression. In the severe group**,** 44.44% had >100 mg/L of CRP value. From this study it was concluded that elevated level of CRP could be included as a potential marker in predicting the severity and possibility of disease progression in non-severe patients with COVID-19, which can help health workers to identify those patients at an early stage for early treatment. Subsequent clinical research with large number sample sizes and CRP level measurements at different treatment times, should be tested to confirm our findings.

The current study encompasses a short sample size which limits the diversity of the study population and it was done in single healthcare setup; therefore, it may lack generalizability and difficult to interpret the statistical significance of the study. As no control group of patients without COVID-19 were included, it would be hard to discern whether the findings are specific to patients with severe symptoms of COVID-19. The retrospective nature of this study was another limitation. Various studies have been done on this topic, but we have tried to collect the data from our hospital setup, as no such study was done from this institute previously. Hence, subsequent clinical studies with larger sample sizes, longer duration and multiple CRP level measurements at different time interval mostly on daily basis at fixed time would be preferable to know the improvement and response of the patient to treatment, should be performed to confirm our findings.

CONCLUSION

CRP is extensively available, affordable, and an easy marker to test. . This suggest CRP testing may be useful as an early index for severe illness and help physicians for treatment. Our findings suggest that serum CRP levels could be used as a crucial indicator to monitor progression and the severity of COVID-19.

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CONFLICT OF INTEREST

The authors declare that that there are no conflicts of interest associated with this manuscript.

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