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Analysis of C-reactive protein level in SARS-CoV-2 patients and its role in predicting the severity of SARS-CoV-2 infection

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Abstract: *Introduction:* Corona Virus Disease-19 (COVID-19) pandemic is a public health emergency due to the spread of 2019 novel Corona Virus (2019-nCoV), also called as Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2). Analysis of CRP along with various other haematological parameters serves as a predictor of infection and inflammation. *Aims and objectives:* The aim of the study was to study the CRP level in SARS-CoV-2 patients and its role in predicting the severity of infection. *Materials and Methods:* As many as 768 patients were included in this study. Serum samples were analysed for CRP levels by Quantitative CRP test, based on the principle of Latex turbidimetry. CRP values equal to or greater than 6mg/L were considered as abnormal. *Results:* Out of 768 serum samples tested, 337 (43.8%) samples showed abnormal values. Out of which 255 (75.7%) were male patients and 82(24.3%) were female patients. A total of 42.4% patients had increased CRP values that belonged to the age group 41-60 years followed by 29% patients that belonged to the age group of 61-80 years. In the age group of 61-80 years 67/98 (68%) patients deteriorated during hospitalization and required mechanical ventilation and the mortality rate was 88% among patients on mechanical ventilation. *Conclusion:* Our study suggested that CRP testing may be useful as an earlier indicator for severe illness and those presenting with marked increase of > 45.6 mg/L should be paid more attention. Male preponderance was detected and elderly patients revealed abnormal values of CRP as compared to young and middle-aged patients.

Keywords: SARS-CoV-2, CRP, Severe illness

Introduction

Corona Virus Disease-19 (COVID-19) pandemic is a public health emergency due to the spread of 2019 novel Corona Virus (2019-nCoV), also called as Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2).COVID-19 is caused by coronavirus belonging to the family of Coronaviridae and the Order Nidovirales [1]. Severity of illness varies from mild to varying severity of pneumonia all the way to acute respiratory distress syndrome (ARDS) and sepsis with multi-organ failure and death [2].

Therefore it is an urgent requirement to assess the severity by investigating various biomarkers. Several studies suggested that in COVID-19 patients there will be various abnormalities in many haematological, biochemical and inflammatory biomarkers with severe disease compared to mild illness [3-5]. These biomarkers can deduct the patients who are in the verge of developing severe disease and helps clinicians to give them proper attention and treatment at the correct time.

The CRP, albumin, LDH (lactate dehydrogenase), neutrophil to lymphocytes ratio, lymphocytes count, procalcitonin, albumin, thrombocytes and ferritin can be used to determine the severity of COVID-19. Decline in lymphocyte, thrombocytes, albumin, and increase in CRP, NLR (neutrophil-lymphocyte ratio), procalcitonin, D-Dimer, ferritin has been reported in COVID-19 patients [1, 5-7]. CRP is an acute-phase protein first described by Tillet and Francis, is synthesized by the liver in response

to interleukin-6 (IL-6) and is a widely available biomarker of inflammation [8]. Recent studies suggested that increase in the levels of CRP can predict disease severity, adverse outcomes, prognosis, and mortality in patients with COVID-19 [9-10]. Thus CRP holds promise as a potential prognostic biomarker which may be helpful to classify patients at early diagnosis and provide prompt treatment.

The objectives of this study were:

1. To study the CRP level in SARS-CoV-2 patients and its role in predicting the severity of SARS-CoV-2 infection
2. To study the association between CRP level and in-hospital mortality.

Material and Methods

This is a retrospective study, conducted for a period of 6months from March 2021 to August 2021 in the Serology section of the Department of Microbiology of a Teaching Tertiary care hospital, Hyderabad that has been designated under COVID-19 hospital during the second wave of SARS-CoV-2. Demographic and epidemiological statistics, such as age, sex, comorbidities and disease history, were gathered upon admission. For laboratory confirmation, real-time reverse transcriptase polymerase chain reaction (RT-PCR) was used as gold standard, according to the recommended protocol of the hospital.

As many as 768 COVID-19 patients as determined by RT-PCR were included in the study. All baseline serum samples were collected immediately after admission for CRP. In this study, we used the following criteria to determine severe cases of SASRS-CoV-2: Respiratory rate ≥30/min, oxygen saturation ≤93%, PaO2/ FiO2 ≤300 mmHg, lung lesions progressed >50% within 24–48 hours, mechanical ventilation was implemented, shock, intensive care unit admission [11].

Estimation of CRP levels: Three to five ml of venous blood was collected from clinically and diagnostically confirmed admitted cases of COVID-19. The serum was separated from the above collected blood samples through centrifugation at 2000 rpm for 10 minutes. Hemolysed and lipemic samples were rejected and hence not included in the study. A Quantitative CRP test, based on the principle of Latex turbidimetry was performed on serum samples by using EURO-CRP TURBILATEX (Asritha Diatech Pvt. Ltd, India). The results were obtained in less than 2 minutes. CRP values equal to or greater than 6 mg/L were considered as abnormal. The procedure and interpretation of results was done according to manufacturer's instructions.

Results

Out of 768 samples, 337 (43.8%) samples revealed abnormal CRP (> 6 mg/L) values. Among them, 255 (75.7%) were males and 82 (24.3%) were females (Figure 1). Among 337 patients with abnormal CRP levels, 207 were diagnosed as non-severe and 130 developed severe/critical disease. In our study, larger number of male patients with abnormal CRP values developed severe disease compared to female patients with abnormal CRP values (Table 1).

Fig-1: Gender Distribution of abnormal CRP values

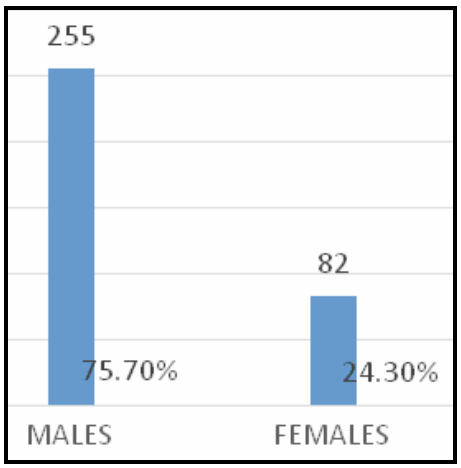

Table-1: Distribution of cases according to non-severe and severe category

Gender	Non Severe	Severe
Males	149	106
Females	58	24
Total	207(61%)	130(39%)

The age wise and gender wise distribution of abnormal CRP values shows Male preponderance (Table 2) and a total of 42.4%

patients had increased CRP values that belonged to the age group 41-60 years followed by 29% patients that belonged to the age group of 61-80 years (Table 2).Associations between CRP concentration and adverse outcomes were consistent in subgroups defined by age and sex (Table 2).The age wise relation with CRP values has also been demonstrated (Table 2).

Table-2: Distribution of abnormal CRP values in different age groups

Age group	Gender		Total (n)	%
	Males	Females		
≤20yrs	02	06	8	2.4
21-40yrs	44	37	81	24.1
41-60yrs	119	24	143	42.4
61-80yrs	84	14	98	29
81-100yrs	06	01	7	2.1
Total	255(75.6%)	82(24.3%)	337(100%)	

Most of the SARS-CoV-2 positive patients had comorbidities, including hypertension (43 %), heart disease (28 %), diabetes (22.3 %), and respiratory diseases (10.4 %) (Table 3). The number of comorbidities was higher in age group of 61-80years (data not shown).

Table-3: Comorbidities in SARS-CoV-2 patients with abnormal CRP levels

Comorbidities	Number of patients	Percentage
Hypertension	133	39.5
Diabetes	75	22.3
Heart diseases	94	27.9
Respiratory diseases	35	10.4

In this study, CRP levels were compared between non-severe and severe groups. In Non-severe group, the median CRP level was 45.6 mg/L vs. 65.7 mg/L in severe group. The median CRP level for those who died was 118 mg/L compared with 61 mg/L among those who survived. Duration for hospital admission to intubation period varied from less than two hours to 10 days. In age group of 61-80years, 67/98 (68%) patients deteriorated during hospitalization and required mechanical ventilation and the mortality rate was 88% among patients on mechanical ventilation (Table 4).

Table -4: Distribution of Survivors and Non-survivors in different age groups

Age Group	Survivors	Non-survivors
≤20years	08	0
21-40years	80	1
41-60years	116	27
61-80years	31	67
81-100years	4	03

Discussion

In the present retrospective study, the clinical characteristics of severe SARS-CoV-2 patients were compared with those of non-severe patients and analysed for the possible factors associated with disease progression and severity. Early monitoring of key indicators for COVID-19 disease progression will place an important role in guiding treatment strategies. CRP is a non-specific acute phase protein and synthesized by hepatocytes when stimulated by inflammation. It binds to a various pathogens, facilitating complement activation through classical pathway [12].

Clinically, increased CRP levels might be an early indicator of hospital acquired infections in COVID-19 patients who were slow to recover, and might help physicians to administer empirical antibiotics treatment early to prevent worsened outcome [13]. Our

study explored the relationship between CRP levels and disease progression in SARS-CoV-2 patients. Results of this study suggested that patients with CRP > 45.6mg/L were more likely to develop severe disease. This result is in line with another study which established disease progression to a severe state due to CRP levels of >41.8 mg/L [14].

The association of high CRP levels with worse outcomes may be due to the severity of the disease consistent with the 'cytokine storm' theory of SARS-CoV-2, where the innate immune system is activated releasing TNF-alpha, IL-6 and IL-1. In addition, an elevated CRP may not be attributable to COVID-19 alone and may represent concomitant pathology such as secondary bacterial pneumonia.

In this study, the age of non-survivors was between 61-80 years, significantly higher than 41-60 years in survivors. Further, age was an independent predictor of adverse outcome, which suggested that old people are more vulnerable to SARS-CoV-2 and more likely to develop severe disease. Similarly, another study also established age factor as predictor of adverse outcome [15].

Our study suggest that all age groups are at risk of acquiring SARS-CoV-2 infection, but elderly people face significant risk of developing severe illness due to physiological changes that occur with ageing and other co morbidities. The increased susceptibility of elderly people with cardiovascular disease and comorbid conditions could also be related to increased concentration of ACE-2 enzyme. Elderly people often have the spectrum of comorbidities that include diabetes, hypertension, renal disease and Chronic Obstructive Pulmonary Disease (COPD) responsible for multiple organ failure during COVID-19 disease [16]. In this study, severity ratio for males was higher than for females. This result is in line with previous studies [15, 17].

Limitation: This study was carried out at single centre, so it may lack generalizability. This is a retrospective study; hence, future studies should focus on multiple CRP level measurements, especially at different treatment times to confirm our findings.

Conclusion

Results suggest that CRP testing may be useful as an earlier indicator for severe illness and those presenting with marked increase of > 45.6mg/L should be paid more attention and help physicians to stratify patients for intense care unit transfer and treatment.

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