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ARTICLE

C-REACTIVE PROTEIN IN COVID-19 - RETROSPECTIVE ANALYSIS OF CLINICAL PROFILE AND OUTCOME AT A TERTIARY CENTRE

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ABSTRACT

Background: *Study the C - reactive protein (CRP) inflammatory marker profile in patients admitted with COVID -19; with emphasis on clinical features, diagnostic and management issues in a major tertiary referral medical college hospital in Vijayapur.* ***Methods:*** *Retrospective analysis of CRP levels in admitted patients with COVID-19 at Al Ameen Medical College and Hospital from July 2020 to December 2020. All patients with COVID- 19 ward admission were included. Serial blood samples for estimating CRP were analyzed at the time of admission, during the hospital stay, and at the time of discharge.* ***Results:*** *Out of 266 patients positive for COVID -19, the mean CRP values during ward hospitalization were raised above 56 mg/L (20-90 mg/L), and the mean CRP during ICU stay was 171 (115 – 300) mg /L. The CRP levels were consistently higher in patients who died compared to those who survived 214 mg/L vs 156 mg/L, p<0.001. CRP levels increased during the first week of hospitalization with a peak on day 3. We had 66 deaths. Compared to patients who died, those who survived had lower peak CRP levels and earlier declines.* ***Conclusion:*** *Derangements in laboratory markers of the inflammatory response are good predictors of clinical severity and complication. CRP can be a good inexpensive marker in resource-poor settings that correlates with disease severity and mortality for effective diagnostic, therapeutic, and prophylactic measures against COVID 19.*

KEY WORDS
COVID-19, C –Reactive Protein (CRP), clinical profile, diagnosis, treatment

INTRODUCTION

COVID-19 is the acronym for the full name coronavirus disease of 2019 caused by the novel coronavirus called SARS-CoV-2. The COVID-19 pandemic began in Wuhan, China in December 2019 and quickly spread to become a global health and economic emergency [1, 2].

COVID-19 presents clinically variably without a set pattern. It ranges from a simple asymptomatic infection to severe pneumonia accompanied by multisystem failure leading to death. The SARS-CoV-2 virus affects all components of the immune system negatively which otherwise would cause viral destruction and recovery. Due to an imbalance of the immune response, there is instead progression of the disease to more severe forms. The Elderly especially with underlying medical issues like heart disease, diabetes, chronic respiratory disease, and cancer are more prone to have negative outcomes [3].

Multiple studies have been conducted to understand the clinical profile and outcomes of hospitalized patients in the SARS- COVID-19 [4-6]. Alterations in markers of the inflammatory response have been identified as predictors of clinical severity and complications [7-9]. The CRP molecule in particular has been identified as an acute-phase, nonspecific marker of inflammation or infection which can be raised in many infectious and non-infectious conditions and can guide prognosis and treatment. In recent studies, the increase in CRP levels has been seen in severe acute respiratory syndrome, Middle East respiratory syndrome, H1N1 influenza [9, 10]. Other recent studies have observed elevated CRP levels COVID-19 patients correlate with severity of disease and disease progression [11]. CRP hence can be considered to be a good potential prognostic biomarker.

The mechanism of rise in CRP levels in severe SARS-CoV-2 remains unknown, but it is hypothesized that it may be associated with host immune responses during infection. Multiple studies suggest that the immune system is impaired during the period of disease that allows the development of viral hyper-inflammation. It was also demonstrated that severe COVID-19 may induce a cytokine storm and lymphocyte damage, as well as suppression of interferon-γ production. The numbers of T cells and B cells further reduce, while the levels of inflammatory cytokines continued to increase in patients with severe disease. Based on these findings, CRP levels could serve as predictive biomarkers for COVID-19 severity. The plasma half-life of CRP is around 19 hours and remains constant in health and disease. The synthesis rate determines the CRP levels, hence reflects degree of the pathological processes stimulating CRP production.

MATERIALS AND METHODS

We conducted a retrospective analysis study of 350 adult patients admitted to the COVID- 19 ward of Al Ameen Medical College and Hospital from July 2020 to December 2020. Inclusion criteria were hospitalized patients above the age of 18 years having SARS-CoV-2 infection confirmed by molecular testing with a minimum of two CRP values within 7 days of admission. Demographic characteristics of age, sex, race, body mass index (BMI), and comorbid diseases were recorded. Admissions in the wards and ICU, length of ICU stay, length of mechanical ventilation and outcome were also recorded. In the first 7 days of hospitalization, peak and mean values of CRP were calculated.

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Statistical Analysis was done with t-tests or by the Mann-Whitney U test. Categorical variables comparison was performed with Pearson's chi-square and Fisher Exact tests. The significant value was considered as $p<0.05$. This study was approved by the Institutional Ethics Committee of Al Ameen Medical College and Hospital. This was a retrospective data analysis during the COVID-19 pandemic. Patient consent and confidentiality was maintained.

RESULTS

In this study, out of total 350 patients, 266 patients fulfilled the inclusion criteria. 36 patients went DAMA (discharge against medical advice). The mean age of patients was 63 years; 119 patients (44.4%) were women. Hypertension (196 [73.5%]), obesity (143 [52.6%]), diabetes mellitus (116[44.0%]), and smoking (72 [26.8%]) were the most common comorbidities [Table 1]. The average duration of hospitalization was 17 (11-28) days. Mean time of ICU stay was 9 days (5-17); 62 patients underwent intubation, and mean time of mechanical ventilation was variable from 12 days to 18 days [Table 2].

Table 1: Demography and Risk profile

Variables	Total patients (n = 266)	Survived (n = 200)	Died (n = 66)	p-value
Age, Mean	63	60	71	<0.001
Sex, Female	119 (44.4%)	94 (46.3%)	26 (38.8%)	0.29
Smoking (Ever),	72 (26.8%)	48 (23.9%)	24 (35.8%)	0.27
Diabetes Mellitus,	116 (44%)	72 (33.8%)	24 (31.3%)	0.23
Hypertension	196(73.5%)	138 (70.6%)	58 (82. 1%)	0.07
Obesity (BMI> = 30kg/m2)	143 (52.6%)	112 (58.2%)	31 (35.8%)	0.002

Table 2: CRP values, Morbidity, Mortality

Variables	Total patients (n = 266)	Survived (n = 200)	Died (n = 66)	p-value
Hospital duration (Median)	17 (11-28)	19 (11-28)	12 (7-16)	<0.001
Length of ICU stay	9 (5-17)	6 (3.5-16)	9 (5-15)	0.94
Duration of intubation	10 (5-14)	10 (5-14)	11 (5-14)	0.95
Died	66 (25%)	-	-	-
CRP (on ICU admission) mg/L	171 (115-300)	156(106-223)	214 (122- 300)	0.17
Mean CRP	126 (82-190)	113 (72-160)	209 (166-289)	<0.001
Max CRP (d l-7)	304 (181-333)	202 (158-262)	309 (249-391)	<0.001

The normal lab range of CRP in our institution was 0-10 mg/L. Out of 266 patients positive for COVID -19, the mean CRP during ward hospitalization, values were raised above 56 mg/L (20-90 mg/L), and the mean CRP on ICU admission was 171 (115 - 300) mg /L. The CRP levels were consistently higher in patients with severe disease and those who died, compared to those who survived [214 mg/L (122 -300 mg/L) vs 156 mg/L (106-223 mg/L), $p<0.001$]. CRP levels increased during the first week of hospitalization with the peak on day 3. We had 66 deaths. Compared to patients who died in whom peak CRP levels were 309 (249-391) mg/l , versus those who survived who had lower peak CRP levels of 202 (158-262) mg/l and earlier recovery.

DISCUSSION

CRP values during hospitalization and rate of CRP change throughout hospitalization seem to be good markers of mortality and correlate well with the length of ICU stay in COVID-19 patients. In studies on the clinical characteristics of coronavirus disease in China by Guan et al most of the patients had elevated levels of C-reactive protein [2]. CRP is a non-specific acute phase inflammatory protein whose expression increases in response to tissue injury, inflammation, and infection [12]. CRP is a readily available marker and inexpensive. The baseline CRP values are determined by factors such as age, gender, lipid profile and smoking [13]. CRP values rise within 24 to 72 hours after exposure to harmful stimuli and decrease exponentially within 18-20 hours after the stimuli have subsided [14]. In patients with sepsis, an increased CRP level> 100 mg /l was identified as an independent predictor for the intensive care unit and 30-day mortality and the length of the intensive care stay in patients [15]. Levels of CRP were seen to be increased in viral respiratory diseases such as SARS, MERS-CoV and H1N1 [16]. Another small retrospective study reported a correlation between mortality and CRP levels in diabetics with COVID-19 [18].

It is observed that CRP levels are elevated in hospitalized COVID-19 patients and correlate with the severity and severity of the disease mortality. Values at admission were independent predictors of disease severity.

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Wang et al in their study on clinical and laboratory data on severe acute respiratory syndrome (SARS) have reported by multivariate analysis, underlying disease and initial CRP level were predictive of death [15].
In studies by Chen et al, different clinical characteristics have been reported between patients with moderate and severe COVID-19. Concentrations of serum high-sensitivity C-reactive protein (hs-CRP) were markedly higher in severe cases than moderate cases [20].

Zhang et al in their study on 140 patients, found significantly more comorbidities (79.3% vs 53.7%, P = .002) with CRP (47.6 vs 28.7, P < .001) in severe cases, compared to non-severe cases [21]. Sharifpour et al. studied C-Reactive protein as a prognostic indicator in hospitalized patients with COVID-19 found the hospitalization-wide median CRP was significantly higher amongst the patients who died, compared to those who survived [206 mg/L (157–288 mg/L) vs 114 mg/L (72–160 mg/L), p<0.001]. An alteration in ≥ 20 units per day of CRP during the first seven days of hospitalization is associated with worse outcomes. CRP levels increased in a linear fashion during the first week of hospitalization and peaked on day 5 [22]. In our study, the peak levels of CRP were on day 3 of hospitalization [Table 3].

Table 3: Comparative analysis with similar studies

Study	No. of cases	Age (yrs)	Sex (M / F)	Study design	Significant CRP values	Outcome	
						Non-severe	Severe
Guan *et al* (2)	1099	47	637/459	Retrospective	≥10 mg/liter	371/658 (56.4%)	110/135 (81.5%)
Wang *et al* (15)	138	52	75/63	Retrospective	7.1 ± 4.0 (mg/dL)	NA	53 (77.9%)
Chen *et al* (20)	21	56	17/4	Retrospective	>60 mg/L	3/9 (33%)	11/11 (100%)
Zhang *et al* (21)	140	57	71/69	Retrospective	>3 mg/L	72/81 (88.9%)	53/55 (96.4%)
Sharifpour M(22)	268	63	149/119	Retrospective	NA	114 mg/L (72–160 mg/L)	206 mg/L (157–288 mg/L)

In our study, mean CRP levels indicate the severity of COVID-19 and are useful as an independent predictor of mortality as evidenced by the finding that the peak CRP levels were significantly higher in the patients who died compared to survivors. The rate at which CRP levels rise during the first seven days of hospitalization is a useful indicator of predicting disease progression and the need for intensive care unit admissions. Elevated CRP levels could correlate with worsening disease due to increased systemic inflammatory responses. Some studies support this position, which suggests that dexamethasone's inhibition of systemic inflammation may reduce COVID-19-related mortality, demonstrating a causal relationship between systemic and clinical inflammation [19]. CRP levels can be used along with other markers of inflammation such as interleukin 6, serum ferritin, and D-dimer levels to monitor response to therapy.

There are limitations to this study. In terms of research methodology, it has been kept relatively simple to reduce strain on patient resources. Though the study is limited in terms of specific association, we have included molecular COVID -RTPCR positive patients to reduce the effects of this drawback. The sample size was relatively sufficient to draw useful conclusions; However, Daily CRP values could not be carried out in all hospitalized patients due to various restrictions.

CONCLUSION

We aimed to analyze the inflammatory responses in COVID-19 and compare it to the clinical presentations, ranging from asymptomatic to severe disease using CRP. Literature review shows elevation of CRP levels in patients with COVID-19 correlates well with the severity and prognosis. The corona pandemic has affected developed and developing countries equally and has caused devastation not seen since the past 100 years. Our aim was to analyze an inexpensive marker that could help in treatment, risk stratification and prognosis. This is important in terms future perspective as the guidelines for diagnosing and treating COVID 19 are being revised continuously as we gain new insights into a virus that has still not been understood with complete clarity. CRP can be a good early marker in resource-poor settings that correlates with disease severity and mortality for effective diagnostic, therapeutic, and prophylactic measures against COVID 19.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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FINANCIAL DISCLOSURE
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