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C Reactive Protein and SARS-CoV-2 Infection Severity A Systematic Review

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ABSTRACT
C reactive protein (CRP) is regarded as an acute phase reactant which is found to be increased in various infections and inflammation. It is produced in liver mainly in response to interleukin 6. It is found to be increased in acute infections of various organs. It also indicates low grade inflammation in human body. In recent pandemic by Severe acute respiratory syndrome corona virus 2 (SARS CoV 2) various biochemical, hematological and inflammatory biomarkers played vital role in diagnosis, prognosis and treatment of Covid-19. Due to its complex nature of presentation, initially researchers explored various biomarkers which could prove useful in better management of the patients. CRP which rises early in Covid 19 infection was one of the most important markers helping in stratification and management of patients. In various studies, CRP was shown to be a severity and mortality indicator in Covid-19 patients. Hence, in this review, we aim to discuss role of CRP in severe and critical patients of Covid-19 infection.

INTRODUCTION

C reactive protein (CRP) is a pentameric protein which is produced by hepatocytes in response to inflammation[1]. Apart from liver, it is also produced by respiratory tract epithelium, alveolar macrophages, smooth muscle cells, lymphocytes and monocytes[2]. Its synthesis is mainly regulated by cytokine IL 6 and IL1which is secreted by visceral adipose tissue[3]. It is regarded as an acute phase reactant produced in response to inflammation and infection. High concentration of CRP can be found in serum in some bacterial infections and levels could increase upto 1000 fold. Elevated levels of CRP are found in infections like appendicitis, cholecystitis, pancreatitis and meningitis[4].

CRP level in blood starts increasing 6-12 hrs after stimulation and continue to increase between 6 and 72 h as a result of both increased synthesis and release from hepatocytes[5]. In 2019 the world witnessed a pandemic due to a respiratory virus called severe acute respiratory syndrome corona virus 2 (SARS CoV 2). The WHO declared it as a global pandemic and named the disease coronavirus disease 19 (Covid-19). The pathogenicity of COVID-19 involves the angiotensin-converting enzyme II (ACE2) which acts as the cellular receptor for SARS-CoV-2 in many human tissues and organs. The viral entrance promotes a downregulation of ACE2 causing proinflammatory signalizations in lungs and other organs[6]. The immune response involves triggering complement pathway leading to cytokine storm which escalates inflammation. ARDS was one of the most common complications of Covid-19 infection[7]. Initial studies of Covid-19 patients suggested CRP to be a diagnostic and prognostic marker and helped to treat the patients accordingly. In this review, we aim to discuss the usefulness of CRP to determine severity of Covid-19 infection.

MATERIALS AND METHODS

Two researchers independently searched electronic database like Pubmed, Google Scholar, Cochrane Library, Web of Sciences, EMBASE, COVID-19 Research Database and Scopus. Search terms used were C reactive protein, biochemical markers, Covid-19, SARS CoV 2, disease severity or prognosis. Then the search was specifically focused on articles which studied laboratory parameters in Covid-19 cases and analyzed severity based on laboratory findings.

Eligibility criteria: We considered the studies which investigated the correlation between biomarker (CRP) and disease severity (Covid-19). The studies which clearly stated type of study, method of diagnosis of Covid-19, classification of patients and outcome were included. Reference method considered for diagnosis was RT PCR. The classification of patients was according to NIH guidelines which categorized them into asymptomatic, mild, moderate, severe and critical illness as per NAAT or antigen testing, clinical features, chest imaging, oxygen saturation, respiratory rate, lung infiltrates, respiratory failure, shock and/or multiple organ failure[8].

We included the studies mentioning confirmed RT PCR positive cases and severe Covid-19 as an outcome. Severe category included individuals who have SpO2 <94% on room air at sea level a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg a respiratory rate >30 breaths/min or lung infiltrates >50%. Critical illness included individuals who had respiratory failure, septic shock and/or multiple organ dysfunctions. The outcome included hypoxia, ARDS, ICU admission or mechanical ventilation. We preferred quantitative CRP estimation over high sensitive CRP.

Quality assessment and data extraction: Two authors independently extracted the data in a standardized format and then was verified by third author. Data included the authors, type of study, cohort size, patient groups, CRP median values, CRP cut off value, area under curve (AUC) and $p<0.05$ for statistical significance.

RESULTS

Initially total 320 articles were downloaded. After removing 35 duplicates, 285 articles were screened for eligibility. A total of 240 studies were excluded after screening titles or abstracts. After evaluating 45 studies, 31 studies were excluded with reasons. (Figure 1). Finally, 14 studies were selected for qualitative synthesis. Thirteen studies were retrospective observational studies and one was prospective cohort. We excluded meta analyses, reviews, case studies and editorials.

C reactive protein and SARS-CoV-2 severity: Due to large number of patients reporting in short time, early diagnosis and appropriate referral was very crucial during pandemic. Detection by RT PCR method largely remained the reference method of diagnosis which was not available at peripheral centers[9]. Many researchers tried to study the use of CRP along with other biomarkers for diagnosing Covid-19 early. The biological profile including CRP, Ferritin and LDH proved to be diagnostic in early stages[10,11].

The complications in severe covid patients included ARDS, acute cardiac injury, venous thromboembolism, acute kidney injury, coagulopathy and shock[12]. Determining disease severity played important role in reducing mortality of Covid-19 patients. The studies, we reviewed, investigated CRP for assessing severity of Covid-19. Most of the AUC (area under curve) findings in these studies show

Table 1: Characteristics of studies reviewed[13-19] CRP- C reactive protein, IL-6- Interleukin 6, IL-10- Interleukin 10, LDH- Lactate dehydrogenase IQR- Inter quartile range, NIV- non invasive ventilation AUC- Area under curve, p<0.05 considered statistically significant, NA- not applicable.

Author	Cohort size	Patient group	CRP median (IQR)	CRP cut-off value	AUC	Sensitivity/specificity	p-value	Other findings/characteristics
Tudorita *et al.*[13]	153	Mild, Moderate, Severe	7.01 (5.05-10.57) 54.14 (16.45-102.9) 99.8 (45.64-166)	76.0 mg L	0.720	0.66/0.712	0.000	CRP best discriminates severe and non- severe form of disease than other inflammatory modulators and classical biomarkers.
Maryame *et al.*[14]	145	Non severe, severe	3.4 (1.08-16.7) 86.4 (21.69-145.8)	10 mg L	0.872	86.3/70.3	< 0.001	On admission, CRP is independent discriminator of severe illness.
Fang *et al.*[15]	140	Mild, severe	Not mentioned	41.8 mg L	0.858	88.9/ 72.7	< 0.001	In multi variant cox model, CRP independently predicts risk of severity
Feliicia *et al.*[16]	125	Mild, moderate, severe	Mean values 19.83 mg L 41.96 mg L 116.67 mg L	NA		NA value	NA	NAOn Spearman test, r- for CRP is 0.496 and p<0.001. One way ANOVA is statistically significant for CRP with form of disease between three groups.
Jian- bo-Xu *et al.*[17]	176	Moderate, severe, critically severe	Not mentioned	52.13 mg L	0.83 0.88/ 0.71		< 0.05 group.	CRP is highest in critical Also, an independent predictor of survival along with Procalcitonin.
S. Keddie *et al.*[18]	100	Hospitalised, oxygen with/without NIV, Ventilated	49.4 73.3 135.5	37 mg L	0.85 0.91/0.66		< 0.05	CRP along with IL- 6, IL-10 and LDH strongly correlated with severity. the progressed to critical illness.

Table 2: Characteristics of studies reviewed[20-26] CRP- C reactive protein, PCT- Procalcitonin, IQR- Inter quartile range, AUC- Area under curve, p<0.05 considered statistically significant

Author	Cohort size	Patient group	CRP median (IQR)	CRP cut- off value	AUC	Sensitivity/specificity	p-value	Other findings/characteristics
Dan Wang *et al.*[20]	143	Moderate, critical	8.6 (4.7-28.6) 54.8 (11.5-100.5)	64.7 mg L	0.77664.8/81.9		<0.001	Cases with CRP >64.7 mg for the progressed to critical stage. L should be closely observed
Chun *et al.*[21]	228	Non severe, severe	3 (0.75-6.82) 7.79 (3.18-12.68)	6.5 mg dL	0.703	59.3/73.9	< 0.001	Upon logistic regression, CRP, PCT, LDH, ferritin and D-dimer were independent predictors of severity.
Sedat *et al.*[22]	106	Mild, severe	25.3(10.6-75.5) 98.5(55.0-149.2)	61.8 mg L	0.778	Not mentioned	<0.001	CRP can be a moderate biomarker for severity of disease
Ferda *et al.*[23]	186	Admitted, not admitted to ICCU	Not mentioned		159.5 mg L	0.82679.5/76.6 LDH	< 0.001	CRP along with D dimer, and Ferritin levels predict risk of both ICCU admission and mortality.
Chaochao *et al.*[24]	27	Initial stage Progression, Peak stage, Recovery stage	Not mentioned	22.42 mg L	0.87 on	83/91	Not mentioned	Patient grouping is based CT scan findings. AUC of CRP to predict severity was higher than CT score.
Wei *et al.*[25]	76	Mild, moderate, severe	Mild- not mentioned Moderate =11.43 Severe= 23.4 according	16.6 mg L	0.898	77/ 72	< 0.001	Patient groups are to CT scan findings. Higher plasma CRP levels indicated severe pneumonia and longer inpatient duration.
Erika *et al.*[26]	123	Severe	9.012 (4.47-14.46)	11 mg dL	0.78 72/ 71		< 0.000	Severe ARDS patient were significantly associated with higher CRP values.

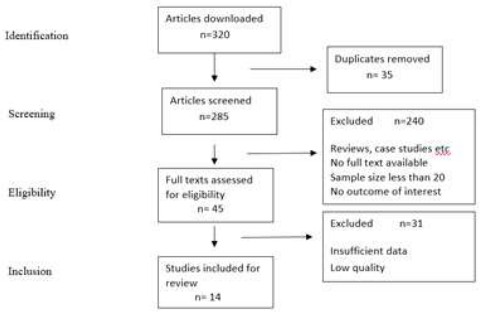

Fig. 1: Process of selection of studies

moderate to strong association between CRP and disease severity. The AUC ranges from 0.703-0.872 in these studies. The cut of value of CRP ranged from 10-159 mg L and gave an indication to consider the patients for close respiratory monitoring or mechanical ventilation beyond these levels. Moreover the cut off values used by various researchers in these studies give high sensitivity and specificity to differentiate severe cases from mild or moderate ones.

The details of the studies reviewed in this paper are mentioned in Table 1 and 2. Tudorita *et al*. (Table 1) compared CRP and other hyperinflammatory markers like IL6, netrophil lymphocyte ratio, platelet lymphocyte ratio, interleukin receptor 1 ß, ESR, ferritin and LDH. The patients were stratified according to disease severity in mild, moderate and severe cases. Among these markers, CRP proved to be best discriminator between severe and non severe form of disease[13]. Maryame *et al*. examined the association between CRP level on admission and disease severity. The AUC of CRP was highest (0.872) in all studies reviewed. The authors concluded that CRP is a robust predictor of adverse disease outcome and also an independent discriminator of severe or critical illness on admission[14]. Fang Liu *et al*. studied CRP, IL 6, and PCT levels on admission by classifying patients into mild and severe form. In this study, authors found that CRP value more than 41.8 mg L and AUC of 0.858 had a high diagnostic value for clinical severity and these patients were more likely to have complications. 15 Felicia *et al*., in a prospective study examined the CRP values in mild, moderate and severe group. They found that CRP values increase with severity of disease which highlights the importance of early estimation of CRP in covid infection[16]. In a retrospective study by Jian Box Xu *et al*., authors had similar observations. They classified the patients into mild, moderate, severe and critically severe groups and found increased trend of CRP in these group and concluded that CRP exhibits an independent increased risk of mortality[17].

Studies carried out by Keddie *et al*. and Jing gong *et al*. evaluated other markers like IL6, IL 10, IL2R, IL 8 and PCT and found that these markers, together with CRP, are strongly associated with disease severity[18,19]. In another study by Dang Wang *et al*. (Table 2) authors measured CRP levels in moderate and severe group of patients and found strong association between CRP and disease severity. They concluded that patients with CRP value more than 64.79 mg L should be closely observed for the progress to critical stage[20]. Along with CRP, other laboratory and hematological markers studied by researchers are LDH, d dimer, Serum Amyloid A, Procalcitonin, ferritin, hsTroponin I and netrophil to lymphocyte ratio. These markers were also strongly associated with disesase severity[21-23]. Chaochao *et al*. classified the patients of covid into initial, peak, progression and recovery stage based on computed topography scan findings. On CT scan, severity was assessed by lung involvement of less than 5%, 6-25%, 26-49%, 50-75% and more than 75% of lung lobes. Authors found that ROC analysis of CRP to predict disease severity was higher than CT scores[24]. Wei chan *et al*., in similar way, grouped the patients based on CT grading into mild (peripheral and subpleural ground glass attenuation) moderate (multiple lobe involvement, ground glass changes, pulmonary consolidation or fibrosis) and severe (diffuse consolidation, minimum 80% involvement or fibrosis) category. Authors found that higher plasma CRP level indicates severe pneumonia and longer inpatient duration[25]. Erika *et al*. in a study of consecutive 123 admissions of covid, correlated the CRP levels with patient's respiratory function evaluated by partial pressure of arterial oxygen to fraction of inspired oxygen. They concluded that, CRP predicts the respiratory failure and suggested closer respiratory monitoring[26].

DISCUSSION

Covid-19, during the pandemic caused 69 million worldwide and 5.3 million deaths in India[27]. In India, the symptomatic patients started reporting from all parts of the country and sudden referral of the patients started to dedicated Covid centers. Developing countries including India had limited ICU beds and early diagnosis and appropriate referral of patients to isolation wards or ICU was crucial. Hyperinflammation plays an important role in severe and critical Covid infection. Cytokine storm is the hallmark of pathophysiology, leading to release of Interleukin 6 which further stimulates production of CRP[28].

Serum CRP and other biochemical and hematological parameters played vital role in assessing the severity of patients in early stage[29,30]. In present review, higher level of CRP was associated with poor outcome. There is variation in cut off value used to

determine severity. The range of 10-159 mg L shows need of detailed study to pursue optimal cut off of CRP to determine poor outcome. The SROC (summary receiver operating characteristics) analysis in a meta analysis showed diagnostic value of = 10 mg L for composite poor outcome[31]. Moreover, CRP level is affected by age, gender, smoking status, weight, lipid levels, blood pressure, and liver injury[32]. Hence, these factors should be considered before interpreting CRP levels. CRP levels reach at peak level at 2-4 days after respiratory tract infections due to various pathogens[33]. Also, absolute CRP concentrations and its velocity of reaching at peak may help to differentiate between bacterial and viral etiology[34]. Hence, interpreting and utilizing CRP values for Covid-19 patients during initial stages of admission was of paramount importance for better outcome. Researchers in meta analyses have found higher levels of CRP in Covid-19 infection in severe group of patients[35,36]. Various meta analyses concluded that CRP level is predictor for severity, is associated with poorer outcome and can help in better monitoring and treatment of patients[37-40].

CONCLUSION

We conclude that C reactive protein is a useful laboratory parameter which helps to determine the severity of Covid-19 infection and its levels help to monitor the progress of the patients. It is better than other classical markers of inflammation and CT scan scores to predict the severity of Covid-19 patients. Hence its early estimation in Covid-19 may help better stratification and management of the patients.

Limitations: Meta analysis of these studies would have helped to find cut off values of CRP to identify severe and critical cases and prioritize further management.

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