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A Review Article on C-Reactive Protein (CRP) As a Biomarker Indicator in Hospitalized Patients with COVID-19 in India

Shubham Bhatnagar*

Department of Community Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, Maharashtra, India

ABSTRACT

Introduction: COVID-19 has been the most widely talked about disease owing to its virulence factors and higher replicability. It has been linked to many conditions such as metabolic distress, fever, dry cough, nausea, dyspnoea, myalgia, inflammatory disease, and autoimmune disorders. Since its discovery as an acute phase super molecule, C-reactive protein is a known general indicator for tissue injury and inflammation.

Objective: To investigate the diagnostic accuracy of CRP in early recognition of severely hospitalized COVID patients.

Methodology: PubMed and Google scholars databases were searched electronically for suitable keywords and 11 publications were shortlisted for this review.

Observations: High CRP levels indicate undergoing inflammation and deterioration in admitted patients. Therefore, high levels indicate poor prognosis if timely intervention is not provided.

Conclusion: Although an increment in C Reactive Protein (CRP) is correlated with death from COVID-19 infection, the findings from different groups are mixed and inconsistent. Yet, the characteristics of high CRP levels (40 mg/L or more) are shown to be positively associated with morbidity and mortality in majority of the cases. This cut off point could help medical practitioners use this biomarker as an early warning sign for better surveillance, planning the course of treatment and care and predicting final outcome.

Its efficacy in detecting the disease in its early stages has been utilized in preventing the fatal effects of COVID-19. In the following review, we sought to assess the accuracy of CRP as a diagnostic as well as prognostic indicator for patients admitted with a severe degree of COVID infection.

Key words: COVID-19, CRP, Prognostic marker

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Corresponding author: Dr. Shubham Bhatnagar
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INTRODUCTION

COVID-19 is well-known for its high virulence factors. The capacity of critical care all over the world has been tested to its extreme potential by this virus induced pandemic. To add to further dismay, the umbrella of symptoms also encompasses neurologic, respiratory, and coagulation problems. The clinical manifestations of COVID-19 infection range from not showing any symptoms to mild degrees of fever, dry cough, dysphagia, dyspnoea, fatigue, and migraine, to more serious complications like pneumonia accompanied by chest pain and hypoxemia. Individuals with signs of mild pneumonia, such as laboured breathing, cough, and high grade pyrexia and blood oxygen (SpO_2) of less than 90% on air exchange have been included in a non-severe cluster. Sufferers with comorbid conditions have a faster progression of the illness. Physiologic diseases, such as hyperglycaemia, in COVID-19 individuals, have been related to greater fatality, particularly in elderly persons.

In several disorders, the C-reactive protein to Albumin Ratio (CAR) has emerged as a prognostic indicator. Since the first time of its inception as an acute phase protein, this ratio has been used as a marker to indicate any damage at the level of tissue as well as inflammation/infection. Here in, we sought to investigate the efficiency of CAR in determining at risk criteria for hospitalized COVID patients with a grave form of disease.

LITERATURE REVIEW

Methodology

We have gathered knowledge from PubMed and Google scholars using main terms such as CRP, biomarker indicator and CRP as prognostic marker in COVID patients.

After gathering data from many articles, this summary report is created.

COVID-19 prevalence and spread

In March 2019, when WHO established COVID-19 as a worldwide pandemic, it had already spread to numerous locations and continents throughout the world, resulting in a community health disaster. With the global increasing rate of COVID-19 cases due to its highly infectious nature, various research have been published on the factors that may be crucial in determining illness severity and treatment efficacy in persons with COVID-19 [1]. The count of infections began to rise exponentially, with many among them having no contact with the animal derived segment, implying that the virus was indeed spreading from one human to human propagation was continuously taking place. Among the many symptoms include fever, dry cough, pain and irritation in throat with shortness of breath, pain in the abdomen, and malaise.

Although many individuals presented with a mild form of infection (as a normal viral flu), evidence of conditions like pneumonia, Acute Respiratory Distress Syndrome (ARDS), and Multi Organ Failure Syndrome (MOFS), and even abnormalities of blood biochemical markers (typically the geriatric and those with comorbidities) has also surfaced. However, there is a significant portion of the population (especially the young population) presenting with an indolent course of the disease. Exceptional molecular assays are used to detect the viral pathogen in respiratory and naso oral discharge. Normal/depleted white cell counts, as well as high C-Reactive Protein, are common test results (CRP) in these patients. It's been speculated that the virus spreads *via* huge droplets produced by individuals with COVID and asymptomatic or mildly symptomatic carriers while coughing and sneezing. Infected droplets have potential to travel up to 10-14 meters and deposit on surfaces, allowing fomites to take forward person to person transmission. The virus may persist on surfaces for 24-72 hours under suitable environmental conditions, however, commonly found disinfectants such as sodium hypochlorite and hydrogen peroxide kill it within a few minutes and provide protection. When a person makes physical contact with the infected surrounding and then encounters the nostrils, mouth or oral cavity, or even eyes, he/she is likely to get the infection. A person exhibiting high grade fever, throat pain, and having recent travel history to/from China, may be presumed a suspect of Coronavirus disease [2]. In the case of a severe infection→antiviral immune response protocol is initiated→inflammatory cytokines released (TNF and interleukins)→cytokine storm→acute lung injury at an interstitial endothelial level→decreased alveo lar surfactant→ARDS/DIC/shock→death.

By April 2021, the world had lost more than 3 million lives to COVID, as per WHO. The adsorption process for the same is 2–14 days following viral exposure. COVID-19 has a lower virulence and a longer initial infection than past Coronavirus infections, such as the Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The symptoms are as follows: Troubled breathing or shortness of breath, continuous chest discomfort or a feeling of heaviness in the chest, lethargy, bluish markings on the lips or face, persistent vomiting/diarrhoea with signs of dehydration can all be warning signs. The most common symptoms as seen in individuals hailing from the epicentre of the infection, Wuhan, in the year 2019 (December) were ARDS of unknown ethology, fever, and weariness. Only a few youngsters had clinical manifestations. The majority of the youngsters were found to be asymptomatic positive for COVID-19. Rare cases of Kawasaki disease like symptoms in the paediatric population undergoing critical care were reported, including hyper inflammatory syndrome and Systemic inflammatory Response Syndrome (SIRS). Inflammatory multisystem syndrome is a disorder complex that affects children. SARS-CoV-2 appears to primarily affect older children, with stomach pain predominating and a higher risk of heart disease and other health problems.

We can use this tool of CRP and CAR assessment to achieve better prognostic results for COVID patients. However, the usefulness of laboratory medicine in early detection, treatment, the standard of care, and prevention initiatives cannot be overstated. Indeed, causative diagnosis of COVID-19 is simply one half of the puzzle; however, we still don't know what causes COVID-19 individuals to have abnormal laboratory results because of its wide spectrum of clinical profiles. Biochemical testing appears to have become increasingly significant in the early course of the disease as it might suggest pathogenicity even before a final diagnosis is made by other methods. Patients with COVID-19 must be tested frequently to detect disease severity and course progression, as well as to analyse the efficacy of chemotherapy [3].

COVID-19 in patients with pre-existing comorbidities

The COVID-19 disease causes a higher admission rate to the Intensive Care Unit (ICU) and death in older patients, especially those 65 and older who have comorbidities and are infected. Patients with comorbidities should take all precautions to minimize contracting SARS-CoV-2, as their prognosis is usually the poorest. High risk patients are those with heart disease, diabetes, immune compromised states as in leukaemia's/lymphomas, Cushing's disease, chronic kidney disease, pneumoconiosis and other pulmonary disorders like COPD, cystic fibrosis, sarcoidosis etc. [4]. Long term consequences include disturbed sleep wake cycles, cognitive impairment, and acute unremitting anergia (ME/CFS representations). The number of COVID-19 patients may increase as a result of the SARS outbreak, culminating in a severe post viral sickness described as "post COVID-19 syndrome," which includes long term chronic fatigue and post exercise neuro immune weariness. Patients with pre-existing cardiovascular conditions are reported to develop hyper coagulation. This might lead to neural stroke or sudden cardiac death.

Patients with diabetes are reported to develop paraesthesia, neural palsies, and even foot drop like illness even after reporting negative for the virus. Other symptoms include deconditioning, muscle atrophy, anxiety, sleeplessness or intense day time sleep, depressive symptoms, lack of self-confidence, 'brain fog' and cognitive impairment [5]. The most probable gateway for viral microbes entering the brain is olfactory pathway which accounts for anosmia and Myalgia Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Populations with pre-existing comorbidities are more prone to succumb to these post COVID manifestations.

C-reactive protein competency in patients with COVID disease in India

It is a necessity to monitor the biochemical parameters of COVID patients to know the rate of progression and treatment protocol. As per literature, individuals having critical symptoms of the disease have significantly increased white cell count, serum creatinine, abnormal hepatic, and renal function tests, elevated C Reactive Protein (CRP) and Interleukin-6 (IL-6), and depleted levels of lymphocytes, and platelets, as well as albumin levels when contrasted to patients with other types of viral flu [3]. CRP, as one of the most well-known acute phase reactants, can spike dramatically when inflammation, endothelial dysfunction, or physical trauma occurs. Inflammatory cytokines such as Interleukin-6 (IL-6) and Interleukin-1 (IL-1) and Tumour Necrosis Factor-alpha (TNF-alpha) are commonly elevated in the circulation during respiratory infections (TNF-alpha). As a result, markedly increased blood CRP levels in non survivors of patients with severe/critical illness demonstrated an excessive inflammatory response in this study, which was consistent with COVID-19 patient's high circulating pro-inflammatory cytokines.

The influence of CRP on disease processes could be linke d to host resistance and inflammatory cascade. In response to inflammatory onset, CRP binds to pathogens and facilitates their evacuation by phagocytic cells, acting as the first line of innate host defence. CRP can also impair neutrophil chemo taxis, a process that possesses anti-inflammatory properties. CRP, on the other hand, can trigger inflammation by enhancing the production of adhesion molecules and pro-inflammatory mediators such as IL-1, IL-6, IL-8, and TNF. Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS) patients' serum CRP levels were shown to be inconsistent (ARDS). Significantly elevated serum CRP levels in COVID-19 patients could indicate exaggerated inflammatory load, which could lead to severe/critical disease or even death. In rare cases, the SARS-CoV-2 infection, as well as the SARS-CoV-2 infection itself, may influence the elevated blood CRP level. Individuals with severe COVID-19, on the other hand, would be well matched by such stacking effects [6].

CRP is a vague but crucial protein produced by hepatocytes and amplified after an acute inflammatory response. CRP's profile has made it a powerful and widely used diagnostic device in medical practice. When comparing Polymerase Chain Reaction (PCR) positive patients to negative controls who merely arrived to a fever clinic with common cold or flu like symptoms that mirror this virus, a CRP level of 4-8 mg/L was found to be beneficial for triaging cases of suspect.

To predict inpatient morbidity, the bulk of this research used CRP with a binary threshold; with recommended levels ranging from 10 mg/L to 76 mg/L. C-Reactive Protein (CRP) was up regulated during COVID-19 [7]. In COVID-19 patients, the median CRP value for the entire hospitalization, in addition to the rate of CRP change over the first seven days, has been determined to be both predictors of death, as well as the duration of ICU, stay. CRP concentrations greater than 100 mg/L were identified as a discrete measure of ICU and 30 day death, in addition to period of ICU stay, in sufferers with sepsis who fulfil septicaemia criteria. CRP concentrations have been documented to connect with disease progression and predict disease development in infectious lung diseases such as H_1N_1, SARS, and also MERS-CoV-2. CRP levels are linked to COVID-19 amplitude and are a major predictor of the risk of mortality. Our findings additionally mean that measuring the trend at which CRP changes over the primary seven days of hospitalization, can be used to expect illness and more aggressive treatment, or the want for an early ICU discharge in case of clinically improving patients. CRP levels rise for 24 to 72 hours after being exposed to an inflammatory response, then drop rapidly after the stimulus has been addressed for 18-20 hours. CRP is a simple, low cost, and widely available test that corresponds with the severity of sickness and death. The peak CRP value for the initial first week was less significant of morbidity than fluctuations in CRP, highlighting the clinical relevance of regular CRP examinations, particularly early in the hospital stay [8].

DISCUSSION

In a recent meta-analysis, elevated CRP, increased LDH, decreased lymphocytes and increased random blood sugar were all found to be substantially relevant to the severity of the condition certain laboratory values (ferritin, pro-calcitonin, and troponin) were shown to be elevated during a cytokine storm may not have been obtained at most clinical laboratories or are only used for studies (IL-6). CRP, albumin, and globulin, on the other hand, are readily available after admission and are often administered at medical centres and, in particular, Intensive Care Units, as part of the admission workup (ICU). An important vital additive of serum protein that impacts systemic inflammation is albumin. Low blood albumin is an independent indicator of mortality in critical patients, indicating poor nutritional status, liver and renal failure. The CRP to albumin ratio upon intake has been associated with increased odds for elderly patients with acute renal insufficiency requiring haemodialysis. Incessant lung infection, cerebrovascular issues, destitute glucose resilience, weight, immune compromised, end stage kidney infection, and liver

infection have all been perceived as potential comorbidities for serious kidney disease ultimately leading to kidney failure [9]

With so much evidence supporting CRP, large randomized trials are needed to see whether the CRP levels we established may be used to risk stratify individuals timely and initiate aggressive therapy with respiratory support and/or corticosteroids medication. In this paper, we have investigated CRP as a predictive marker in COVID-19 patients in the current Indian scenario.

Now that pathophysiology of the novel COVID-19 is somewhat better understood, with its affinity for the ACE-2 receptors and specific enzymes (furin and trans membrane protease serine 2) on the hair cells and Schwann cells that aid the SARS-CoV-2 viral fusion with the host cell, It is high time than ever to find more novel biomarkers to identify COVID-19 infections that may progress adversely in adults and children. Most hospitals that interact with COVID-19 cases need to be capable of measuring these biomarkers and have them rapidly and all time accessible. The proposed ratios (albumin to globulin and CRP to albumin) appear to be more accurate than each value individually and could be used in the initial evaluation of patients who have tested positive by PCR. There is a greater need to find novel biomarkers to recognize COVID-19 instances that may progress poorly in teens and adults. Most hospitals that deal with COVID-19 patients need to be able to assess these biomarkers and have them available [9].

CRP was the most powerful single laboratory predictor. COVID-19 does not yet have a specific antiviral medication, and the mortality rate remains high. Furthermore, the COVID-19 mortality rate was much greater in servicing kidney transplant recipients [10,11].

CONCLUSION

Other Coronavirus infections in the Middle East have been documented. In those with COVID-19, respiratory illness was linked to a lower absolute lymphocyte count and a normal or slightly lower white blood cell count. However, clinical clinicians' capacity to stratify risk at the time of patient admission continues to be a key challenge in dealing with this condition. Normal count of white blood cell, neutrophils, platelets and reduced count of lymphocytes, albumin while elevation in CRP, pro-calcitonin, and LDH and D-dimer were the hallmark features of COVID-19 in maintenance haemodialysis patients. It was observed that the individuals who died due to infection had higher counts of neutrophil, white blood cell, CRP, LDH and pro-calcitonin levels as compared to those who survived, although albumin levels were significantly lower. Upon history taking of a suspected case of COVID-19, during haemodialysis elevated CRP and pro-calcitonin may suggest a subsequent bacterial infection. With the changing trend of disease, there arises a need for more accurate diagnostic and prognostic markers.

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