Original Article

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Biochemistry Section

Analysis of C-reactive Protein and Ferritin as Inflammatory Marker and their Association with the Severity of COVID-19: A Cross-sectional Study

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ABSTRACT

Introduction: Virus-induced hyperinflammation can lead to mild symptoms or multiorgan dysfunction in severe Coronavirus Disease-2019 (COVID-19). In contrast to moderate conditions, severe COVID-19 exhibits higher levels of inflammatory markers, and tracking these markers may enable early disease detection and a good prognosis. The role of ferritin and C-reactive Protein (CRP) as inflammatory markers is evident in literature. However, it has not been proven whether this differs between patients who COVID-19 and non COVID-19 patients.

Aim: To compare CRP and ferritin levels between COVID-19 positive patients and apparently normal Reverse Transcription-Polymerase Chain Reaction (RT-PCR) negative individuals, and to assess their association with COVID-19 severity.

Materials and Methods: A cross-sectional study was conducted in isolation wards and Intensive Care Units (ICUs) at a Tertiary Care Hospital in Government Medical College Manjeri, Kerala, India. The study was conducted over six months, from August 2020 to January 2021. A total of 70 patients diagnosed with COVID-19 and 35 RT-PCR negative healthy subjects, aged between 18-75 years, were included. CRP and ferritin levels were measured and compared between COVID-19 patients and apparently normal RT-PCR negative individuals. The quantitative parameters were evaluated using the Mann-Whitney U test, and the categorical values were analysed using the Chi-square test. Statistical significance was defined as a p-value of ≤0.05.

Results: All COVID-19 patients were between the ages of 18 and 75 years, with a mean age of 55.03±13.01 years in symptomatic COVID-19 positive (group A), 57.89±10.85 years in COVID-19 positive with pneumonia (group B), and 40.89±15.89 years in the control group (group C). In group A, there were 18 (51%) males and 17 (49%) females, while in group B, 23 (66%) were males and 12 (34%) were females. Out of the 35 control group participants, 17 (49%) were males and 18 (51%) were females. No significant differences were reported when comparing the genders of patients with healthy subjects. The results of the present study showed significantly higher median values of CRP (34.90) and ferritin (652.20) in COVID-19 patients compared to non-COVID-19 individuals, which were 4 and 116, respectively (p-value<0.001).

Conclusion: Increased levels of CRP and ferritin in COVID-19 patients suggest that they can be used as inflammatory markers for the early detection of the disease. Moreover, higher levels in individuals with severe symptoms, as opposed to those with mild symptoms, define their involvement in illness severity.

Keywords: Acute-phase proteins, Coronavirus disease-2019, Hyperinflammation, Pneumonia

INTRODUCTION

COVID-19 is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and was first detected in a Hospital in Wuhan, China on 29th December 2019 [1]. With the rapid spread of the outbreak, the World Health Organisation (WHO) announced it as a public health emergency of international concern [2]. This infection has led to a pandemic that has affected millions worldwide [3]. The majority experience mild to moderate respiratory symptoms and recover without any special management; however, seriously ill patients require medical attention and hospitalisation. Serious illness is more likely to affect older individuals and those with underlying medical disorders such as Diabetes Mellitus (DM), chronic respiratory conditions, cardiovascular diseases, or malignancies [4]. Early diagnosis is vital, considering the short time of onset of Acute Respiratory Distress Syndrome (ARDS) after admission to the hospital and the high mortality rates in COVID-19 [4]. The inflammatory process due to SARS-CoV-2 infection may play a main role in the pathogenesis of multiple organ damage and be responsible for the dramatic outcome of COVID-19 patients. Serum ferritin is a well-known acute-phase reactant, levels of which increase in various acute and chronic inflammatory conditions such as Still's disease [5], rheumatoid arthritis [6], and multiple sclerosis [7]. Regardless of the underlying pathology, hyperferritinemia is associated with high mortality [8]. Moreover, ferritin is a marker of significant macrophage activation. In mouse models, during immune responses, activated macrophages produce more ferritin, leading to elevated serum ferritin levels in the circulation [9]. Human Cluster of Differentiation 4+ (CD4+) and CD8+ T lymphocytes and CD19+ B lymphocytes express H-ferritin binding sites, which are positively associated with the proliferative status of these immune cells [10].

The CRP is an exquisitely sensitive systemic marker of acute phase response in inflammation, infection and tissue damage, which could be used as a indicator of inflammation. It is another produced by the liver. CRP binds to the phosphocholine expressed on the surface of bacterial cells, such as pneumococcal bacteria, activating the complement system and promoting phagocytosis by macrophages, which clears necrotic and apoptotic cells and bacteria [11]. When the inflammation subsides, CRP levels may return to the normal range. It remains stable in vivo, except for occasional spikes related to subclinical or minor inflammation, infections, or trauma [12].

During the course of COVID-19 pneumonia, a cytokine response storm can be triggered, which is associated with high mortality in COVID-19. Cytokines such as Interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha stimulate hepatocytes to produce CRP [13]. A previous study by Chen R et al., showed that CRP is a biomarker strongly correlated with COVID-19 progression [14]. Several retrospective comparison studies by Liu F et al., and Kumari S et al., revealed an increasing trend of acute-phase proteins, including CRP, procalcitonin, and IL-6, in non survivors and a stable or downward trend in survivors [15,16].

Additionally, this is one of the first comparative cross-sectional studies evaluating CRP and ferritin as inflammatory markers in Malappuram district, Kerala, India. Hence, the present study was conducted to compare these two parameters in COVID-19 patients and COVID-19 RT-PCR negative individuals, and to assess their association with COVID-19 severity.

MATERIALS AND METHODS

A cross-sectional study was conducted in the isolation ward and ICU of a Tertiary Care Hospital at Government Medical College Manjeri, Kerala, India, for a period of six months, from August 2020 to January 2021. Institutional Ethical Clearance was obtained (IEC number IEC/GMCM/48), and written informed consent was obtained from all the subjects.

Inclusion criteria: All symptomatic patients aged between 18 and 75 years who tested positive for COVID-19 were included. Symptoms included fever and/or sore throat or cough. Those presenting with fever and/or respiratory symptoms, Oxygen Saturation (SpO_2) <94%, and chest x-ray findings suggestive of lung infection were diagnosed as having COVID-19 pneumonia [17]. Subjects aged between 18 and 75 years who were admitted for diseases other than COVID-19 and RT-PCR negative on RT-PCR were chosen as controls.

Exclusion criteria: Those with associated co-morbidities such as uncontrolled diabetes, hypertension, or heart disease were excluded from the study population and comparison group.

Sample size calculation: Considering a power of 80% and an error of 5%, based on a previous study [18], the calculated sample size was 33 subjects in each group.

$$n=\frac{(Z\alpha+Z\beta)^2\ SD^2}{d^2}$$

n=(Zα+Zβ)2 SD2d2

Zα=1.96 for an error of 5%

Zβ=0.84 for a power of 80%

SD, the pooled standard deviation=22.5

d, the difference in means=11

Study Procedure

A total of 70 COVID-19 patients were divided into 35 symptomatic COVID-19 patients (group A) and 35 COVID-19 patients with pneumonia (group B) and compared against 35 RT-PCR negative healthy individuals. After obtaining written informed consent, 5 mL of venous blood was collected in plain tubes from both cases and controls for CRP and ferritin estimation. CRP was measured by a fully automated biochemistry analyser using latex turbidimetry. A value of 6 mg/L was used as the reference value, and samples with CRP levels >6 mg/L were reported as positive [18]. Values between 6 mg/L and 100 mg/L were considered as mild to moderate elevation, and values >100 mg/L were considered as severe elevation [19]. The normal range for ferritin was taken as 24-285 µg/L in males and 12-270 µg/L in females. Values above 285 µg/L in males and >270 µg/L in females were considered as high values [20]. In case serum ferritin and CRP levels were assessed at the time of admission, on the 3rd day, and on the 7th day of hospitalisation.

STATISTICAL ANALYSIS

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) version 25.0 by International Business Machines (IBM). Since the data was not normally distributed, it was presented as the median. The quantitative parameters were evaluated using the Mann-Whitney U test, and the categorical values were analysed using Analysis of Variance (ANOVA) and the Chi-square test. A p-value < 0.05 was considered to be statistically significant.

RESULTS

All 70 COVID-19 patients were aged between 18 and 75 years, with a significantly higher mean age compared to healthy individuals. In group A, there were 18 (51%) males and 17 (49%) females, while in group B, there were 23 (66%) males and 12 (34%) females. Out of the 35 individuals in the control group, 17 (49%) were males and 18 (51%) were females. There were no significant differences observed when comparing gender of patients with healthy people [Table/Fig-1].

Variables	Group A (n=35) Mean±SD	Group B (n=35) Mean±SD	Group C (n=35) Mean±SD	p-value
Age (in years)	55.03±13.01	57.89±10.85	40.89±15.89	<0.001
Gender distribution	**n (%)**	**n (%)**	**n (%)**	
Males	18 (51)	23 (66)	17 (49)	0.303
Females	17 (49)	12 (34)	18 (51)	

[Table/Fig-1]: Comparison of age between group A, B and group C by one-way ANOVA and gender distribution by Chi-square test (N=105).

The median values of CRP and ferritin were significantly higher in COVID-19 patients compared to healthy individuals [Table/Fig-2]. Significantly higher levels of CRP and serum ferritin were found in group B on admission and day three, compared to group A, suggesting that they play a major role in the severity of the disease. However, a significantly higher level of serum ferritin in group B compared to group A was observed only on the seventh day, indicating that ferritin may be a better predictor of disease severity than CRP [Table/Fig-3].

Variables	Groups		p-value
	Group A+B (n=70)	Group C (n=35)	
	Median (Q1, Q3)		
CRP	34.90 (5,139.75)	4.00 (3,5)	<0.001
Ferritin	652.20 (293.52,1120.50)	116.00 (88,170)	<0.001

[Table/Fig-2]: Comparison of CRP and ferritin between COVID-19 positive (group A+B) and normal subjects (group C) on admission using Mann-Whitney U test (N=105). CRP: C-reactive protein

Variables	Groups		p-value
	Group A	Group B	
	Median (Q1, Q3)		
On admission			
CRP	16.1 (5,84.2)	55 (20,192)	<0.001
Ferritin	436 (210,786)	804 (394,1514)	<0.001
Day 3rd			
CRP	14.40 (5,64)	36.00 (13,121)	0.011
Ferritin	480 (232,861)	803 (406,1772)	0.015
Day 7th			
CRP	12.90 (5,80)	24 (5,125)	0.105
Ferritin	412 (229,600)	700 (473,1365)	0.002

[Table/Fig-3]: Comparison of CRP and ferritin in symptomatic COVID-19 positive (group A) and COVID-19 with pneumonia patients positive (group B) on admission, third and seventh day using Mann-Whitney U test.

On admission, it was found that 20 (36%) patients had a normal level of CRP, 31 (100%) had a mild to moderate elevation, and 19 (100%) had a severe elevation in CRP levels. In the RT-PCR negative

group, all 35 (100%) individuals had a normal level of CRP, and this difference between cases and controls was found to be statistically significant [Table/Fig-4]. In the present study, 15 (30%) patients had a normal level of serum ferritin, and 55 (100%) had a higher level of serum ferritin. In the RT-PCR negative group, all 35 (100%) healthy individuals had a normal level of serum ferritin. The difference in the distribution of serum ferritin levels between the cases and controls was found to be statistically significant [Table/Fig-5].

Groups	CRP level			χ^2	p-value
	Normal n (%)	Mild to moderate n (%)	Severe n (%)		
Group A+B (n=70)	20 (36)	31 (100)	19 (100)	47.72	<0.001
Group C (n=35)	35 (64)	0	0		

[Table/Fig-4]: Categorisation of COVID-19 patients using CRP on the day of admission by Chi-square test.

Groups	Ferritin level		χ^2	p-value
	Normal n (%)	High n (%)		
Group A+B (n=70)	15 (30)	55 (100)	57.75	<0.001
Group C (n=35)	35 (70)	0		

[Table/Fig-5]: Categorisation of COVID-19 patients using ferritin on the day of admission by Chi-square test.

DISCUSSION

COVID-19 has become one of the most common causes of morbidity and mortality in recent years [1]. Early monitoring of key indicators such as CRP and ferritin is important for assessing the severity of a patient's condition and guiding treatment strategies. In the present study, CRP and ferritin levels were significantly higher in COVID-19 patients compared to non-COVID-19 patients. Additionally, a significant difference in age was observed between the cases and controls, which might be due to a low incidence in young adults and a higher need for hospitalisation among middle-aged and elderly individuals compared to young adults. In general, older people are more susceptible to infections. Persistent viral infections can trigger monoclonal expansion of T cells, resulting in poor variability of memory T cells over a lifetime. This ultimately leads to immune exhaustion due to a decline in T cell diversity [21]. Moreover, the severity of respiratory illness might be associated with age-related changes in the physical properties of the lungs and a decline in immune function, known as immunosenescence. The mechanical defenses of the lungs, such as cough, the barrier function of mucus and epithelium, and mucociliary clearance, along with the innate immune system, help to clear aspirated or inhaled substances, including infectious agents. However, these actions are known to decrease with aging [22]. Santesmasses D et al., also stated that SARS-CoV-2 tends to preferentially affect elderly people and those with pre-existing conditions due to an elevated age-related expression of Angiotensin Converting Enzyme 2 (ACE2) in the lungs [23].

The SARS-CoV-2 virus infects human cells by attaching its membrane Spike (S) protein to ACE2. An age-related increase in the expression of this gene, along with depletion of antiviral defenses, contributes to a higher damaging effect in the lungs caused by the coronavirus. Additionally, different tissues have varying levels of ACE2 gene expression, which can lead to complications other than pneumonia, such as diarrhea observed in COVID-19 positive patients. However, it is important to note that while ACE2 is involved in SARS-CoV-2 infection, it also plays a protective role in the lungs, as postulated by Monteil V et al., [24]. These findings are consistent with recent publications, including the study by Banchini F et al., [25].

Serum ferritin has traditionally been studied as a marker of iron metabolism, but it has gained importance as a marker of inflammation in COVID-19, as demonstrated in the present study and previous research by Banchini et al., [25]. Elevated levels of ferritin can indicate cellular damage, particularly when levels exceed 600 ng/mL, suggesting a link between ferritin production and organ damage. In severe cases, this can result in cell death known as ferroptosis, leading to acute respiratory distress syndrome (ARDS) that shares similarities with COVID-19 pneumonia. Increased ferritin levels suggest the development of a cytokine storm as a result of inflammation [26]. Furthermore, Kernan KF and Carcillo JA stated that individuals with a hyperferritinemic phenotype exhibit a characteristic pattern of activation in the reticuloendothelial system and multiple organ dysfunction [27]. This phenotype is typically associated with a recessive genetic disorder called Familial Hemophagocytic Lymphohistiocytosis (FHLH), characterised by excessive macrophage activation. The cascade of events seen in this disorder is driven by interferon-γ, resulting from inherited defects in cytotoxic T lymphocyte and non-killer cell-mediated cytolytic killing. Patients with inflammatory conditions other than FHLH can also present with macrophage activation syndrome, including viral or bacterial sepsis and systemic inflammatory response syndrome, as well as inherited immunologic disorders. These conditions are pathobiologically linked through a pattern of extreme hyperferritinemia and elevated cytokines.

Another research study by Farid E et al., revealed that ferritin and CRP levels are higher in severe pneumonia patients compared to those with mild to moderate pneumonia, and even higher in asymptomatic COVID-19 patients. This indicates that these biomarkers can accurately predict patients who are at risk of developing severe COVID-19 infections and COVID-19 pneumonia [28]. COVID-19 patients with moderate elevations in CRP levels may have some reversible tissue damage associated with the natural response to combat the viral disease. At this stage, therapeutic considerations may include the use of antimicrobials and immune modulation using interferon therapies or biologic agents that can neutralise proinflammatory factors, in addition to viral neutralisation therapies. Patients with significantly elevated CRP levels may have advanced tissue damage and pathologies associated with cytokine storm, coagulation abnormalities, and multiple organ failure. High CRP levels would correlate with a life-threatening prognosis [19]. The role of CRP in inflammation has been well described by Fazal M [29]. The authors explained that CRP exists in two unique isoforms: native CRP (nCRP) and monomeric or modified CRP (mCRP). At sites of infection, inflammation, and tissue damage, the nCRP isoform can irreversibly break down into five mCRP subunits. Depending on the isoform of CRP released and active during infection and inflammation, it exhibits both proinflammatory and anti-inflammatory effects. CRP exerts proinflammatory effects by releasing nitric oxide and cytokines, and anti-inflammatory effects by mediating the activation of the complement pathway, apoptosis, and phagocytosis. CRP plays a major role in recognizing self and non self molecules, leading to activation of the adaptive immune system in infectious and inflammatory diseases. Ahnach M et al., also supported the role of CRP levels as a sensitive and early indicator of COVID-19 severity [30]. During infectious or inflammatory disease states, CRP levels can activate the classical complement pathway and modulate the activity of phagocytes, thereby assisting in opsonisation of infectious agents and dead or dying cells. Therefore, acute-phase proteins such as CRP and ferritin can serve as early biomarkers of inflammation and for the early diagnosis of pneumonia in COVID-19.

Limitation(s)

A comprehensive laboratory score that includes inflammatory, biochemical, and hematological parameters should be considered, along with clinical parameters, to predict the severity and prognosis of COVID-19 patients and improve clinical management and prevention of serious complications. In the present study, only CRP and ferritin were used as an attempt to assess the severity of the disease.

CONCLUSION(S)

The present study concluded that serum ferritin and CRP levels were elevated in patients with COVID-19 compared to individuals who tested negative for RT-PCR. Additionally, the levels of these parameters were higher in patients with pneumonia compared to those with mild symptoms. Therefore, they can be used for early detection and isolation of suspected patients, which is crucial in controlling the COVID-19 outbreak and for prognosis. As the present study was based on a small sample size, there may be some limitations, and the authors suggest that future research should be conducted on a larger population. Furthermore, more research is needed to determine the independent predictive role of CRP and ferritin in disease severity.

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