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Estimation of D-dimer, C-reactive protein and ferritin in Covid-19 survivors in and around areas of Lucknow, India

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ABSTRACT

Background: The novel coronavirus disease (COVID-19), caused by SARS-CoV-2, is highly contagious and was initially thought to primarily affect the upper respiratory tract. However, it is now known to impact multiple organ systems. Critically ill COVID-19 survivors often experience hyperinflammation, and associated biomarkers may be valuable for risk stratification.

Objective: This study aimed to estimate the levels of key biomarkers, including serum C-reactive protein (CRP), D-dimer, and serum ferritin, in COVID-19 survivors to help mitigate further disease complications and associated mortality.

Methods: A case-control study was conducted involving COVID-19 survivors and a control group with no history of COVID-19. D-dimer and ferritin levels were measured using a Mini Vidas Immunoassay Analyzer, while CRP levels were assessed using a Dimension RXL Siemens autoanalyzer based on Particle Enhanced Turbidimetric Immunoassay.

Results: The findings revealed that CRP levels were significantly higher in COVID-19 survivors compared to controls ($p < 0.0001$). Additionally, D-dimer and ferritin levels were also significantly elevated in COVID-19 survivors compared to controls (both $p < 0.0001$).

Conclusion: The study demonstrated that COVID-19 survivors have substantially higher levels of CRP, D-dimer, and ferritin than controls, highlighting the potential importance of these biomarkers in monitoring and managing long-term complications in this population.

Keywords: C-reactive protein, D-dimer, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), serum ferritin

Introduction

The global pandemic of Coronavirus Disease 2019 (COVID-19) posed a significant threat to global public health [1]. The causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel single-stranded RNA beta coronavirus that shares approximately 79% nucleotide similarity with SARS-CoV [2-5]. COVID-19 presents a wide spectrum of clinical severity, ranging from asymptomatic cases to severe pneumonia, acute respiratory distress syndrome (ARDS), and even death [6]. Consequently, effective monitoring of COVID-19 severity and early intervention are essential for reducing mortality [6].

Accumulating evidence suggests that inflammatory responses play a critical role in the progression of COVID-19 [7,8]. The inflammatory responses triggered by SARS-CoV-2 replication and cellular damage recruit macrophages and monocytes, leading to the release of cytokines and chemokines [9]. These, in turn, attract and activate immune cells, potentially resulting in cytokine storms and subsequent disease

exacerbation [10]. Several inflammatory markers have shown promise in predicting disease severity and mortality [11]. Among these, C-reactive protein (CRP), serum ferritin, and interleukin-6 (IL-6) have been significantly associated with an elevated risk of severe COVID-19 [12-14].

CRP, an acute-phase protein, rapidly increases in the bloodstream during infection and is strongly linked to acute inflammation and coronary heart disease [15]. Severe inflammation is a primary cause of critical illness and death in COVID-19 patients, with elevated serum CRP levels serving as a key indicator of such inflammation. A cytokine response storm (CRS), often triggered during COVID-19 pneumonia, is associated with high mortality rates [16]. CRP production is upregulated when hepatocytes are stimulated by cytokines such as IL-6 and TNF-α, making CRP a crucial biomarker for tracking disease progression in COVID-19 [17-18]. CRP has been strongly correlated with the onset of stroke and elevated levels of acute-phase reactants in COVID-19 patients [19]. Individuals with acute ischemic stroke who also had COVID-19 exhibited higher levels of D-dimer, fibrinogen, and CRP, indicating a systemic hyperinflammatory and hypercoagulable state [20]. Notably, CRP not only serves as an indicator of inflammation but also contributes to the pathogenic process.

Furthermore, SARS-CoV-2 infection-induced inflammation and hypoxia can cause endothelial cell dysfunction, promoting thrombosis and raising D-dimer levels [21]. Elevated D-dimer is associated with poor prognosis, particularly when complications such as deep vein thrombosis, disseminated intravascular coagulopathy, and pulmonary microthrombus arise [22-25]. Serum ferritin, traditionally an indicator of iron metabolism [26], has also emerged as an important biomarker of inflammation in COVID-19 [27]. Ferritin levels are generally elevated in all types of inflammatory responses [28], and high ferritin levels in COVID-19 are associated with the release of proinflammatory cytokines, cellular damage, and secondary tissue injury.

COVID-19 is a systemic inflammatory condition characterized by elevated levels of pro-inflammatory markers (e.g., CRP) and pro-inflammatory cytokines (e.g., IL-6, TNF-α) [29-31]. High ferritin levels associated with COVID-19 are believed to result from the release of pro-inflammatory cytokines (e.g., IL-6, IL-1β, and TNF-α), cellular damage, metabolic acidosis, free radical production, and secondary tissue damage. Individual studies have reported that in COVID-19 survivors, serum ferritin correlates with disease severity and its surrogates, such as CRP [32].

Studies suggested that COVID-19 survivors with elevated levels of inflammatory biomarkers may face long-term complications or late-onset health issues. Therefore, we aimed to estimate the levels of serum CRP, D-dimer, and serum ferritin in COVID-19 survivors to better understand and mitigate potential disease complications and associated mortality.

Methods

Subject selection

This case-control study was conducted following approval from the Institutional Ethical Committee at the Integral Institute of Medical Sciences and Research, Lucknow. A total of 84 adult subjects were included, comprising 42 cases and 42 controls, all of whom met the inclusion criteria. Demographic details and clinical histories for each subject were collected using a standardized proforma.

Inclusion criteria for cases

The case group consisted of individuals who were diagnosed COVID-19 survivors, specifically those who had recovered from COVID-19 within the past year. Diagnosis of COVID-19 was confirmed through RT-PCR or Rapid Antigen tests and further validated by a physician. The study included COVID-19 survivors aged 35 to 60 years, who had no comorbidities and were not receiving hormonal steroids, diuretics, or any other therapy. All selected survivors had experienced mild to moderate COVID-19 illness without requiring oxygen therapy. Initial clinical details of these survivors were obtained from the Department of

Table 1. Demographics in control subjects and cases

Parameters	Control (n=42),	Cases (n=42)	P-value
Age (years)	42.88±9.13	40.50±7.17	0.19
Gender (M/F)	21/21	21/21	1.00
C reactive protein (mg/L)	1.22±0.91	8.96±4.28	<0.0001
D-dimer (ng /mL)	0.30±0.21	1.50±0.61	<0.0001
Serum ferritin (ng/mL)	146.48±56.94	224.11±80.4	<0.0001

*p<0.05 considered statistically significant Data represented as mean ± SD

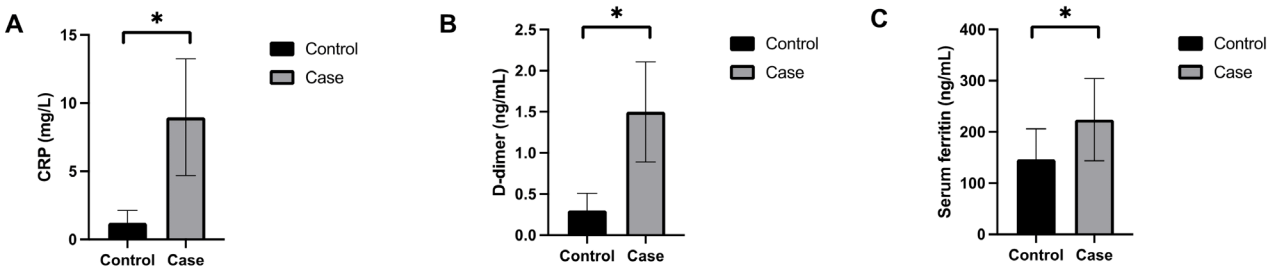

Figure 1. Biochemical parameters in control subjects and cases. (A) C-reactive protein (CRP), (B) D-dimer, (C) Serum ferritin. *p<0.05 considered statistically significant; data represented as mean ± SD

Medical Records at University Hospital, and they were subsequently contacted for serum sample collection for laboratory investigations.

Inclusion criteria for controls

The control group consisted of healthy individuals from the general population, aged 35 to 60 years, with no history of COVID-19.

Laboratory investigations

A total of 5 mL of venous blood was collected from each subject under aseptic conditions. D-dimer and ferritin levels were measured using the Biomerieux Mini Vidas Immunoassay Analyzer (Biomerieux Inc., France), which operates on the principle of enzyme-linked fluorescent assay (ELFA). All assays were performed according to the manufacturer's instructions. The normal reference range for D-dimer is less than 500 ng/mL, and for ferritin, it is 70 to 350 ng/mL.

C-reactive protein (CRP) levels were measured using a particle enhanced turbidimetric immunoassay (PETIA) with a commercially available kit (Transasia Bio-Medicals Ltd., Erba Diagnostics, Mannheim, Germany). The assay was conducted according to the manufacturer's protocol. The normal reference range for CRP in adults is less than 5 mg/L.

Statistical analysis

Statistical analysis was conducted using IBM SPSS version 20.0. Data are presented as Mean ± SD. An unpaired t-test was used to compare variables between the control and case groups. Pearson's correlation coefficient was calculated among the cases to assess the relationships between different parameters. A p-value of less than 0.05 was considered statistically significant.

Results

The study included a total of 84 subjects, comprising 42 controls and 42 COVID-19 survivors, all aged between 35 and 60 years (Table 1). The results indicated that the mean CRP level was significantly higher in COVID-19 survivors compared to controls ($p < 0.0001$). Similarly, the mean D-dimer level was significantly elevated in the cases compared to the controls ($p < 0.0001$). The mean serum ferritin level was also significantly higher in the cases than in the controls ($p < 0.0001$) (Figure 1).

Table 2. Pearson's correlation coefficient test of various parameters among cases

Parameters	CRP (mg/L)	Serum ferritin (ng/mL)	D-dimer (ng/mL)
CRP (mg/L)	1	-0.150	-0.067
Serum ferritin (ng/mL)		1	0.470**
D-dimer (ng/mL)			1

*Correlation is significant at the 0.05 level (2tailed)).
CRP: C-reactive protein

Additionally, a positive correlation was observed between ferritin and D-dimer levels among the cases ($r = 0.470$, $p < 0.05$) (Table 2) The study included a total of 84 subjects, comprising 42 controls and 42 COVID-19 survivors, all aged between 35 and 60 years. The results indicated that the mean CRP level was significantly higher in COVID-19 survivors compared to controls ($p < 0.0001$). Similarly, the mean D-dimer level was significantly elevated in the cases compared to the controls ($p < 0.0001$). The mean serum ferritin level was also significantly higher in the cases than in the controls ($p < 0.0001$), as detailed in Table 1. Additionally, a positive correlation was observed between ferritin and D-dimer levels among the cases ($r = 0.470$, $p < 0.05$).

Discussion

The results of this study revealed that COVID-19 survivors had significantly higher mean levels of CRP, D-dimer, and ferritin compared to the controls. A significant positive correlation was observed between ferritin and D-dimer among the cases. SARS-CoV-2 infection can lead to endothelial dysfunction due to hyperinflammation and hypoxia-induced damage, which may promote thrombosis and elevate D-dimer levels. Recent studies have indicated that D-dimer can be a useful predictor of COVID-19 mortality [33-35]. CRP, a biomarker associated with the progression of COVID-19, is markedly elevated in the early stages of inflammation [36]. In COVID-19 patients, CRP levels have been strongly correlated with the onset of stroke and peak levels of acute-phase reactants [37].

Elevated ferritin levels indicate an active monocyte-macrophage system, with ferritin synthesis in these cells being influenced by cytokine status at both the transcriptional and translational levels [38]. Studies have shown that COVID-19 survivors with acute renal damage have higher serum ferritin levels [39]. Clinical observations have also found that COVID-19 survivors with acute ischemic stroke exhibit elevated concentrations of D-dimer, fibrinogen, and CRP, suggesting a systemic hyperinflammatory and hypercoagulable state [40].

COVID-19 affects nearly all vital organs, and its effects can persist for a long time. Long-term clinical findings indicate that D-dimer, fibrinogen, and CRP levels remain elevated in COVID-19 survivors with acute ischemic stroke. These elevated levels may contribute to cellular and endothelial dysfunction across various organs. Assessing D-dimer, ferritin, and CRP levels in COVID-19 survivors could play a significant role in early detection and management of potential complications, as these biomarkers were found to be elevated in most COVID-19 non-survivors compared to survivors during the pandemic [41-43].

Conclusion

The study demonstrated that D-dimer, ferritin, and CRP levels were significantly elevated in COVID-19 survivors compared to controls. Additionally, a significant positive correlation was observed between D-dimer and ferritin levels among the survivors. Regular monitoring and detection of these inflammatory markers may be beneficial for early screening and prevention of further complications in COVID-19 survivors.

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Declaration of interest

The authors declare no conflict of interest.

Author contributions

CS: data collection and analysis, drafted the manuscript. DT: conception or design of work, analysis and interpretation of results. SK: conception or design of work, analysis and interpretation of results. HJ: analysis and interpretation of results. MMK; conception or design of work, analysis and interpretation of results. SP: conception or design of work, drafted the manuscript. RA: conception or design of work, analysis and interpretation of results. All authors approved the final version of the manuscript for submission and publication.

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