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Original Article

Association of Acute Phase Reactants with COVID-19-related Severity and Mortality: A Study in a Tertiary Care Hospital in India

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ABSTRACT

Background and Objectives: The outbreak of coronavirus disease 2019 (COVID-19) has become a public health emergency. This study aimed to investigate a possible correlation between COVID-19 severity and mortality and serum levels of ferritin and C-reactive protein (CRP).

Methods: This retrospective descriptive study was conducted on 75 COVID-19 patients hospitalized in a tertiary care hospital in Central Karnataka (India) from April 2021 to June 2021. Demographic details as well as clinical and laboratory parameters were retrieved from hospital records.

Results: Of 75 patients, 50 were survivors and 25 were non-survivors. Serum ferritin levels were significantly associated with mortality (p<0.040). There was no significant association between CRP level and COVID-19 severity or mortality (p>0.05).

Conclusion: This study revealed that serum ferritin levels can be used as a prognostic marker for COVID-19 patients.

Keywords: COVID-19 Testing, Hyperferritinemia, C-Reactive Protein.

INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) pandemic began in Wuhan, China. In India, the first confirmed case of COVID-19 was identified in January 2020 in Kerala, and according to official figures, India has the second-highest number of COVID-19 cases and the third-highest number of COVID-19-related deaths (1). The causative agent was identified by next-generation sequencing as a novel coronavirus, from the samples received from patients with pneumonia. In the early stages, patients develop acute respiratory symptoms, and few developed acute respiratory failure and other serious complications (2). In mild to moderate cases, symptomatic treatment and isolation are required, but in severe patients, intensive care unit admission is required. Thus, early assessment of risk factors for critical illness is crucial for reducing the mortality of COVID-19 patients (3). Although the disease has spread rapidly in India, a limited number of studies in the country have investigated the markers of severity and mortality of COVID-19. Some laboratory investigations have found a connection between poor outcomes of COVID-19 and acute phase reactants or inflammatory biomarkers, such as serum ferritin and C-reactive protein (CRP) (4). This study investigates the possible association between inflammatory biomarkers and COVID-19 severity and mortality.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted at a tertiary care center in JJM Medical College, Davangere, Karnataka, India. The study received approval from the Institutional Ethical Committee of JJM Medical College, Davangere, Karnataka (IEC Registration No- ECR/731/Inst/KA/2015/RR-18 issued under rule 122DD of the Drug & Cosmetics Rules 1945. Ref No:- JJMMC/IEC-24-2021). The study included 75 COVID-19 cases who had been hospitalized between April and July 2021. Demographic and clinical characteristics of the patients including age, sex, co-morbidities, and laboratory parameters (serum ferritin and CRP levels) were retrieved from medical records. Inclusion criterion was having a positive RT-PCR for COVID-19. Patient who received repeated blood transfusion and had hemochromatosis were excluded from the study.

All categorical variables were expressed as percentages. To study the association between variables, the chi-square test or Fisher's exact test was used. Continuous variables were expressed as mean and standard deviation. The unpaired t-test was used to compare normally distributed variables, and the Mann-Whitney U test was used to compare non-normally distributed variables. All analyses were carried out in IBM SPSS software (version 21), and a *p*-value of <0.05 was considered statistically significant.

RESULTS

Of 75 hospitalized COVID-19 patients, 25 cases (33.3%) were non-survivors and 50 (66.7%) were survivors. In addition, 45 cases (60%) had a mild-to-moderate disease, while 30 cases (40%) had severe disease. As expected, the severity of the disease was significantly associated with the outcome (p<0.001) (Table 1).

Table 1- Association of severity of the disease with outcome in COVID-19 patients

Severity	The outcome of the disease		Total
	Survivors	Non-survivors	
Mild-moderate	38 (84.4%)	7 (15.6%)	45(60%)
Severe	12 (40%)	18 (60%)	30 (40%)
Total	50 (66.7%)	25 (33.3%)	75 (100%)
Chi-square test p<0.001, highly significant			

Table 2- Social demographics, serum ferritin, and CRP levels of COVID-19 survivors and non-survivors

Demographics		Outcome		Total	*p*
		Survivors	Non-Survivors		
Age (years)	≤50	29 (80.5%)	7 (14.5%)	36 (48%)	<0.05
	≥50	21 (53.8%)	18 (46.2%)	39 (52%)	
Sex	Male	28 (62.2%)	17 (37.8%)	45 (60%)	>0.05
	Female	22 (73.3%)	8 (26.7%)	30 (40%)	
Comorbidities	Present	27 (60%)	18 (40%)	45(60%)	>0.05
	Absent	23 (76.7%)	7 (23.3%)	30(40%)	
Serum ferritin	Normal	14 (87.5%)	2 (12.5%)	16(21.3%)	<0.04
	Raised	36 (61%)	23(39%)	59(78.7%)	
CRP	Normal	10(83%)	2(17%)	12 (16%)	>0.05
	Raised	40(63.4%)	23 (36.6%)	63	

Serum CRP is a non-specific, acute-phase protein induced by interleukin-6 in the liver and a sensitive biomarker of inflammation, There was a significant positive association between age and the outcome of the disease. The average age was 51.10 years in recovered patients and 58.76 in non-survivors. There was no significant association between sex and the outcome of the disease. Of 75 cases, 45 (60%) had associated comorbidities including diabetes mellitus (n=29) and hypertension (n=29). Other comorbidities were chronic obstructive pulmonary disease, asthma, tuberculosis, infective heart disease, chronic kidney disease, and one case of thrombolytic disorder. However, there was no significant association between comorbidities and disease outcome (Table 2).

Laboratory findings of the patients on admission revealed that serum ferritin was raised in 59 cases (78.7%) out of which 23 cases (39%) were non-survivors. Serum ferritin was normal in 16 cases (21.3%) out of which 2 (12.5%) were non-survivors. The mean level of serum ferritin in non-survivors (755.29 ng/mL) was higher than in non-survivors (531.88 ng/mL) in survivors.

There was a significant association between serum ferritin levels and mortality (p=0.04 value), but there was no significant association between serum ferritin levels and severity of the disease (p=0.075). The CRP level was raised in 63 cases (84%), among them 40 (63.4%) recovered and 23 (36.6%) died of the disease. Serum CRP was normal in 12 cases (16%), among them only 2 (17%) were non-survivors, and 10 (83%) recovered from the disease. Serum CRP had no significant correlation with the outcome or severity of the disease (p>0.05) (Table 3).

Table 3- Correlation of serum ferritin and CRP levels with severity of COVID-19

Parameters	Severity				Mann-Whitney U test	
	Mild-moderate		Severe		P-value	Significance
	Mean	Std. Deviation	Mean	Std. Deviation		
Ferritin (ng/mL)	533.88	458.62	715.05	503.07	0.075	Not significant
CRP					0.50	Not significant
	102.30	179.78	85.23	85.55		

DISCUSSION

Severe acute respiratory syndrome coronavirus 2 (SARS‑CoV‑2) is a novel coronavirus that generally causes mild respiratory disease, but there is the possibility of progression to severe pneumonia, which can lead to multiorgan failure and death. The main aim of this research was to find the association of the acute phase reactants i.e. CRP levels and serum ferritin levels with the severity and outcome of COVID-19. Our analysis showed that serum ferritin levels were elevated in non-survivors and significantly associated with mortality. However, we found no correlation between the severity of the disease and serum ferritin. In addition, CRP levels were elevated in both survivors and non-survivors, but there was no correlation between CRP levels and severity or mortality.

Serum ferritin level increases during viral infections and can act as a marker of viral replication (5). In a study on 5,700 hospitalized COVID-19 patients in New York City, ferritin levels were pathologically high (6). This is in line with our findings and the results of a study in China (7). Anemia and hyperferritinemia, regardless of the underlying pathology, are strong predictors of mortality (8, 9). Anemia could be the result of iron-restricted erythropoiesis arising from alterations in iron metabolism.

Hyperferritinemia could be indicative of a strong inflammatory reaction in COVID-19 or viral entry into the human body and its impact on iron metabolism (10, 11). According to Rosario et al., the clinical picture of critical cases of COVID-19 resembles macrophage activating syndrome, which is commonly associated with high levels of ferritin or even cytokine storm (12, 13). Zhou et al. also revealed that the increase in ferritin levels is associated with the worsening of exacerbated COVID-19 symptoms (14). A previous study concluded that serum ferritin levels are strongly associated with the severity and prognosis of COVID-19 (4). Taneri et al. revealed a significant difference in mean ferritin levels between survivors and non-survivors, which is similar to our findings (15).

infection, and tissue damage. Elevated CRP is associated with cardiovascular disease, acute kidney injury in surgical patients (16), and inflammatory rheumatic diseases such as rheumatoid arthritis and gout (17). In a study by Chen et al., 84% of the patients with severe illness had high CRP levels (> 150 mg/L) (18). Shekhanawar et al. concluded that CRP levels are strongly associated with the severity and prognosis of COVID-19 (4) However, we observed no significant association between CRP levels and COVID-19 severity or outcome.

CONCLUSION

Serum ferritin level is significantly associated with mortality in COVID-19 patients. Moreover, CRP level has no significant association with COVID-19 severity or mortality. .Our findings also revealed that serum ferritin levels can be used as a predictor of prognosis in COVID-19 patients. Further clinical studies should be performed to clarify the prognostic value of these biomarkers.

Limitations

Our study had some limitations. First, our sample size was small. We described a modest-sized case series of hospitalized patients. To better define the clinical course of the disease, natural history, and risk factors for mortality, the collection of data from a larger cohort would be appropriate. Second, serum ferritin and CRP levels were taken on admission. It would be relevant to investigate the changes in these two markers over time to confirm their correlation with the prognosis and severity of COVID-19.

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DECLARATIONS

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Ethics approvals and consent to participate

The study received approval from the Institutional Ethical Committee- J.J.M.Medical College, Davangere, Karnataka (IEC Registration No- ECR/731/Inst/KA/2015/RR-18 issued under rule 122DD of the Drug & Cosmetics Rules 1945. Ref No:- JJMMC/IEC-24-2021).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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