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Inflammatory Parameters in COVID-19: A Retrospective Study in a Tertiary Care Centre in Eastern India

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ABSTRACT

Background: *The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused the recent pandemic of coronavirus disease 2019 (COVID-19). Inflammatory responses play a critical role in the progression of COVID-19. It is important to identify early manifestations of COVID-19 patients who are at risk for disease progression and manage them accordingly. In this study, we aimed to determine the inflammatory markers viz. C-reactive protein (CRP), D-dimer, procalcitonin, ferritin, and IL-6, in COVID-19 patients and compare these parameters between discharged (after recovery) and expired patients. We also looked for any association between these parameters and the number of days of hospitalization of the discharged (after recovery) patients.* ***Methods:*** *We conducted a retrospective observational study on 50 COVID-19 patients. The level of inflammatory markers viz. CRP, D-dimer, Procalcitonin, Ferritin, and IL-6 of the patients were recorded. The patients were divided into two broad categories: - Group A: Discharged from hospital after recovery; Group B: expired at hospital. Group A was divided into Group A1: Discharged from hospital after recovery, number of days of hospitalization ≤ 10; Group A2: Discharged from hospital after recovery, number of days of hospitalization>10.* ***Results:*** *Patients in group B (nonsurvivors) had significantly higher serum levels of D-dimer, procalcitonin, and ferritin than group A (survivors).* ***Conclusions:*** *High serum levels of D-dimer, procalcitonin, and ferritin can predict worse outcomes in COVID- 19 patients.*

Keywords: COVID-19, C-reactive protein (CRP), D-dimer, Ferritin, IL-6, Procalcitonin, Severe Acute Respiratory Syndrome-CoV-2

INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has caused the recent pandemic of coronavirus disease 2019 (COVID-19). This disease has made major public health and economic impact [1]. The clinical spectrum of COVID-19 is varied. The patients can be asymptomatic carriers or they can develop severe, bilateral, and diffuse pneumonia, leading to Acute Respiratory Distress Syndrome (ARDS), respiratory failure, and multiple organ dysfunction [2,3]. The common clinical features of COVID-19 are cough, fever, dyspnea, fatigue, myalgia, headache, anosmia, ageusia, and diarrhoea [4,5]. SARS-CoV-2 spreads among people through direct contact routes and by droplet and airborne transmission. It is important to identify early manifestations of COVID-19 patients who are at risk for disease progression and manage them accordingly. This will alleviate the major stress on healthcare systems.

Inflammatory responses play a critical role in the progression of COVID-19 [6]. Inflammatory responses are induced by rapid viral replication of SARS-CoV-2 and cellular destruction. There is the recruitment of macrophages and monocytes and the release of cytokines and chemokines. These cytokines and chemokines then attract immune cells and activate immune responses, leading to cytokine storms and aggravations [7]. Several inflammatory markers can

detect disease severity and fatality. Inflammatory markers such as procalcitonin, serum ferritin, D-dimer, C-Reactive Protein (CRP), and Interleukin-6 (IL-6) have been reported to be significantly associated with the high risks of the development of severe COVID-19 [8,9]. However, these results remain controversial due to no observed difference in their levels by other studies [10,11].

The early stage of COVID-19 may be associated with high D-dimer, Prolonged Prothrombin Time (PT), and elevated levels of fibrinogen, indicating activation of coagulation pathways and thrombosis. Studies have reported a 3-fold to 4-fold rise in D-dimer levels is linked to poor prognosis. In addition, underlying diseases such as diabetes, cancer, stroke, and pregnancy may trigger an increase in D-dimer levels in COVID-19 patients [12].

Procalcitonin is a glycoprotein without hormonal activity and the precursor of calcitonin. Serum procalcitonin levels are usually low or undetectable. They are increased in bacterial infections and relatively low in viral infections and, therefore, can be used to distinguish between bacterial and viral infections [13].

Increased serum ferritin caused by excessive inflammation is associated with high mortality and represents an indication to recognize high-risk patients to guide the therapeutic intervention to control inflammation. Serum ferritin, a feature of hemophagocytic lymphohistiocytosis, which is a known complication of viral infection, is closely related to the poor recovery of COVID-19 patients [14].

CRP is a non-specific acute-phase protein induced by IL-6 in the liver and a sensitive biomarker of inflammation and tissue damage. CRP expression level is usually low but increases rapidly and significantly during acute inflammatory responses. The elevation of CRP in isolation or combination with other markers may reveal bacterial or viral infections.

Lionte, et al. demonstrated that inflammation biomarkers, when performed on admission and predischarge, in a cohort of noncritically ill COVID-19 hospitalized patients throughout successive pandemic waves, showed a moderate predictive value for 30-day mortality and modest predictive value for post-acute long COVID-19. Among inflammation biomarkers, CRP had the best performance [15].

In this study, we aimed to determine the inflammatory markers *viz*. CRP, D- dimer, procalcitonin, ferritin, and IL-6, in COVID-19 patients and compare these parameters between discharged (after recovery) and expired patients. We also looked for any association between these parameters and the number of days of hospitalization of the discharged (after recovery) patients.

METHODS

We conducted a retrospective observational study at Desun Hospital. It included 50 COVID-19 patients admitted to our institution, from July 2020 to September 2020. This study was approved by the ethics committee of our institute. Data about the patients were retrieved from institutional archives.

The study included Real-Time Polymerase Chain Reaction (RT-PCR) confirmed SARS-CoV-2 infected patients. Patients who had haematological malignancies and immunodeficient states were excluded from the study. Clinical data about the cases such as age, sex, signs, and symptoms as well as relevant history were obtained from medical records. The level of inflammatory markers *viz*. CRP, D-dimer, Procalcitonin, Ferritin, and IL-6 of the patients were recorded.

The RT-PCR confirmed SARS-CoV-2 infected patients were divided into two broad categories based on the outcome, Group A: Discharged from hospital after recovery; Group B: expired at hospital. Group A was further divided into Group A1: Discharged from hospital after recovery, with the number of days of hospitalization ≤ 10; Group A2: Discharged from hospital after recovery, with the number of days of hospitalization >10. The cut-off for high CRP, high D-dimer, high procalcitonin, high ferritin, and high IL-6 was 10 mg/L, 200 ng/ml, 0.05 ng/ml, 300 ng/ml, and 6 pg/ml respectively.

The values of CRP, D-dimer, procalcitonin, ferritin, and IL-6 of the RT PCR confirmed SARS-CoV-2 infected patients were expressed as mean and range. These variables were compared between group A and group B, and group A1 and group A2 using an unpaired-test-two-tailed. Categorical variables were expressed as percentages, and compared between the groups using Fischer's exact test or Chi-square test. All statistical analyses were done using GraphPad Prism 6Tm. The p-value is <0.05 and was considered to be statistically significant.

RESULTS

Our study included 50 patients. The mean age of the patients was 61.9 years (range: 27 years-89 years). 37 patients (74%) were male and 13 patients (26%) were females. Group A included 40 (80%) patients and group B included 10 (20%) patients, respectively. The mean age of patients in group A was 59.6 years (range: 27 years-89 years) and that in group B was 70.7 years (range: 62 years-85 years) (p=0.01). Group A1 and group A2 included 26 (65%) and 14 (35%) patients, respectively. The mean age of patients in group A1 was 60.6 years (range: 27 years-89 years) and that in group B was 57.9 years (range: 32 years-79 years) (p=0.5). Among males, 29 (78.3%) patients were discharged while 8 (21.7%) patients died. Among females, 11 (84.6%) patients were discharged while 2 (15.4%) patients died.

The mean D-dimer of group A was 233.3 ng/ml (range: 150 ng/ml-400 ng/ml) and that of group B was 360 ng/ml (range: 200 ng/ml-400 ng/ml) (p=0.02). 90% (9 out of 10) of patients in group B had D-dimer 200 ng/ml while in group A, 62.5% (25 out of 40) had d- Dimer ≥ 200 ng/ml (p=0.1). The mean procalcitonin of group A was 0.194 ng/ml (range: 0.02 ng/ml-1.12 ng/ml) and that of group B was 1.376 ng/ml (range: 0.16 ng/ml-3.51 ng/ml) (p=0.03). 100% (10 out of 10) of patients in group B had Procalcitonin ≥ 0.05 ng/ml while in group A, 90% (36 out of 40) had procalcitonin ≥ 0.05 ng/ml (p=0.5). The mean ferritin of group A was 693.3 ng/ml (range: 3 ng/ml-2666 ng/ml) and that of group B was 1105 ng/ml (range: 329 ng/ml -2000 ng/ml) (p=0.1). 100% (10 out of 10) of patients in group B had ferritin ≥ 300 ng/ml while in group A, 65% (26 out of 40) had ferritin ≥ 300 ng/ml (p=0.04). The mean CRP of group A was 105 mg/L (range: 3 mg/L-313 mg/L) and that of group B was 180.8 mg/L (range: 51 mg/L-359 mg/L) (p=0.09). 100% (10 out of 10) of patients in group B had CRP ≥ 10 mg/L while in group A, 85% (34 out of 40) had CRP ≥ 10 mg/L (p=0.3). The mean IL-6 of group A was 77.43 pg/ml (range: 1.5 pg/ml-930 pg/ml) and that of group B was 141.9 pg/ml (range: 13 pg/ml-512 pg/ml) (p=0.2). 100% (10 out of10) of patients in group B had IL-6 ≥ 6 pg/ml while in group A, 30% (12 out of 40) had IL-6 ≥ 6 pg/ml (p=0.9) (Table 1 and Table 2).

The mean D-dimer of group A1 was 218.18 ng/ml (range: 150 ng/ml-400 ng/ml) and that of group A2 was 257.14 ng/ml (range: 200 ng/ml-400 ng/ml) (p=0.3). 66.7% (10 out of 15) of patients in group A2 had D-dimer ≥ 200 ng/ml while in group A1, 60% (15 out of 25) had D-dimer ≥ 200 ng/ml (p=0.7). The mean procalcitonin of group A1 was 0.1384 ng/ml (range: 0.02 ng/ml-0.70 ng/ml) and that of group A2 was 0.3410 ng/ml (range: 0.07 ng/ml-1.12 ng/ml) (p=0.1). 100% (15 out of 15) of patients in group A2 had procalcitonin ≥ 0.05 ng/ml while in group A1, 84% (21 out of 25) had procalcitonin ≥ 0.05 ng/ml (p=0.3). The mean ferritin of group A1 was 599.6 ng/ml (range: 3 ng/ml-2666 ng/ml) and that of group A2 was 867.3 ng/ml (range: 10.20 ng/ml-1917 ng/ml) (p=0.2). 60% (9 out of 15) of patients in group A2 had ferritin ≥ 300 ng/ml while in group A1, 68% (17 out of 25) had ferritin ≥ 300 ng/ml (p=0.7). The mean CRP of group A1 was 96.50 mg/L (range: 3-313 mg/L) and that of group A2 was 122 mg/L (range: 3 mg/L-292 mg/L (p=0.4). 80% (12 out of 15) of patients in group A2 had CRP ≥ 10 mg/L while in group A1, 88% (22 out of 25) had CRP ≥ 10 mg/L (p=0.6). The mean IL-6 of group A1 was 74.30 pg/ml (range: 1.5 pg/ml -930 pg/ml and that of group A2 was 82.97 pg/ml (range: 1.5 pg/ml -279 pg/ml) (p=0.8). 80% (12 out of 15) of patients in group A2 had IL-6 ≥ 6 pg/ml while in group A1, 64% (16 out of 25) had IL-6 ≥ 6 pg/ml (p=0.5) (Table 1 and Table 2).

Table 1 Comparison of mean and range of CRP, D- dimer, Procalcitonin, Ferritin and IL-6 between group A and group B and between group A1 and group A2

	Comparison between group A and group B			Comparison between group A1 and group A2		
	Group A (Discharged)	**Group B (Death)**	**p-value**	**Group A1 (Hospitalisation ≤ 10 days)**	**Group A2 (Hospitalisation >10 days)**	**p-value**
Mean CRP (mg/l)	105	180.8	0.09	96.5	122	0.4
Range of CRP (mg/l)	3-313	51-359		3-313	3-292	
Mean D-dimer (ng/ml)	233.3	360	0.02	218.18	257.14	0.3
Range of D-dimer (ng/ml)	150-400	200-400		150-400	200-400	
Mean Procalcitonin (ng/ml)	0.194	1.376	0.03	0.1384	0.341	0.1
Range of Procalcitonin (ng/ml)	0.02-1.12	0.16-3.51		0.02-0.70	0.07-1.12	
Mean Ferritin (ng/ml)	693.3	1105	0.1	599.6	867.3	0.2
Range of Ferritin (ng/ml)	3-2666	329-2000		3-2666	10.20-1917	

Mean IL-6 (pg/ml)	77.43	141.9	0.2	74.3	82.97	0.8
Range of IL-6 (pg/ml)	1.5- 930	13-512		1.5-930	1.5-279	

Table 2 Comparison of CRP, D-dimer, Procalcitonin, Ferritin and IL-6 between group A and group B and between group A1 and group A2.

	Comparison between group A and group B			**Comparison between group A1 and group A2**		
	Group A (Discharged) [N=10]	**Group B (Dead) [N=10]**	**p-value**	**Group A1 (Hospitalization |≤ 10 days) [N=25]**	**Group A2 (Hospitalisation >10 days) [N=15]**	**p-value**
CRP						
CRP<10 mg/L	6 (15%)	0	0.3	3 (12%)	3 (20%)	0.6
CRP ≥ 10 mg/L	34 (85%)	10 (100%)		22 (88%)	12 (80%)	
D-dimer						
D-dimer<200 ng/ml	15 (37.5%)	1 (10%)	0.1	10 (40%)	5 (33.3%)	0.7
D-dimer ≥ 200 ng/ml	25 (62.5%)	9 (90%)		15 (60%)	10 (66.7)	
Procalcitonin						
Procalcitonin<0.05 ng/ml	4 (10%)	0	0.5	4 (16%)	0	0.3
Procalcitonin ≥ 0.05 ng/ml	36 (90%)	10 (100%)		21 (84%)	15 (100%)	
Ferritin						
Ferritin<300 ng/ml	14 (35%)	0	0.04	8 (32%)	6 (40%)	0.7
Ferritin ≥ 300 ng/ml	26 (65%)	10 (100%)		17 (68%)	9 (60%)	
IL-6						
IL-6<6 pg/ml	12 (30%)	0	0.09	9 (36%)	3 (20%)	0.5
IL-6 ≥ 6 pg/ml	28 (70%)	10 (100%)		16 (64%)	12 (80%)	

DISCUSSION

Even though most cases have mild symptoms and a good prognosis, COVID-19 can develop into ARDS and even death. To date, there is no effective therapy for COVID-19. Therefore, it is important to identify the markers that monitor the progression of the disease and treat patients early. Several studies have shown increased proinflammatory cytokines in the serum of COVID-19 patients. Anti-inflammatory agents for COVID-19 therapy highlight the critical role of inflammation in the progression of COVID-19 [6]. However, the role of inflammatory markers in monitoring the severity of COVID-19 is still controversial.

It has been well documented that abnormal D-dimer helps indicate deep venous thrombosis in cardiovascular diseases [16]. We analyzed the correlation between D-dimer level and clinical prognosis in the patients. Only one of the patients had cardiovascular disease. The mean D-dimer of non-survivors was more than that of survivors (p=0.02). Li, et al. found that among patients without cardiovascular disease, non-survivors had significantly higher d -dimer levels than survivors [17]. Zhang et al showed that D-dimer on admission greater than 2.0 µg/mL could effectively predict in-hospital mortality in patients with Covid-19, which indicated D- dimer could be an early and helpful marker to improve the management of Covid-19 patients [18].

We reported the mean procalcitonin levels of non-survivors to be more than that of survivors (p=0.03). Studies have shown that procalcitonin levels are over four times higher in severe patients than in moderate patients and over eight times higher in critical patients than in moderate patients. For discharged patients, both high-normal procalcitonin levels and abnormal procalcitonin levels decrease during recovery. In cases where the patients have succumbed, serum levels of procalcitonin have increased as the disease worsened. Procalcitonin may be an indicator of disease severity in COVID-19 and serial procalcitonin measurements may be useful in predicting the prognosis [19].

The overall number of COVID-19 patients with increased procalcitonin values is limited. A meta-analysis suggests

that serial procalcitonin measurement may play a role in predicting progression towards a more severe form of the disease. The production of procalcitonin and its release into the circulation is enormously amplified during bacterial infections, actively sustained by enhanced concentrations of interleukin -1β, tumour necrosis factor-α, and IL-6. The synthesis of procalcitonin is inhibited by interferon-γ, whose concentration increases during viral infections. Therefore, the procalcitonin value remains within the reference range in several patients with non-complicated SARS-CoV-2 infection. Its substantial increase reflects bacterial coinfection in those developing severe forms of the disease, thus contributing to complicating the clinical picture [20].

100% of the non-survivors in our study had ferritin ≥ 300 ng/ml while 65% of survivors had ferritin ≥ 300 ng/ml (p=0.04). A meta-analysis revealed the role of ferritin in indicating a severe disease and a mortality risk in COVID-19. It also showed that COVID-19 patients who were at higher risk because of comorbidities including diabetes, thrombotic complication, and cancer showed a higher level of ferritin than that COVID-19 patients without the same comorbidities [14]. Zhou, et al. reported that the increase in ferritin level was associated with the worsening of COVID-19 [21].

Circulation ferritin level increases during viral infections and can be a marker of viral replication. Increased levels of ferritin due to cytokine storm have also been reported in severe COVID-19 patients. During the cytokine storm in COVID-19, many inflammatory cytokines are rapidly produced, which stimulate hepatocytes, Kupffer cells, and macrophages to secrete ferritin. The dysfunctional immune response associated with macrophage activation and the thrombotic storm finally leads to multiple organ damage. The cytokine storm and the exaggerated host immune response i.e., ferritin participate in the development of ARDS [14].

In our study, although 100% of the non-survivors had CRP ≥ 10 mg/L, there was no significant difference in CRP between survivors and non-survivors. In the study by Chen et al., no statistically significant difference was found in the level of CRP between the non-severe and the severe group [10]. Other studies have reported CRP levels to be positively related to the severity of COVID-19 [8]. Ponti, et al. found CRP to be significantly increased in the initial phases of the infection for severe COVID-19 patients and an early predictor for severe COVID-19 [9].

In our study, although 100% of the non-survivors had IL-6 ≥ 6 pg/ml, there was no significant difference in IL-6 between survivors and non-survivors. IL-6 has been reported to be significantly increased in non-survivors versus survivors. The significant increase of IL-6 is connected to Cytokine Storm and can lead to further tissue damage. This hyperbolic systemic inflammation relates to lymphopenia and is associated with severe disease [9].

Lionte et al, in their study, showed that CRP correlated with 30-day mortality in noncritically ill COVID-19 patients. Ferritin and fibrinogen showed comparative performance with IL-6 for post-acute COVID-19 [22].

CONCLUSION

We observed that COVID-19 can lead to alterations in inflammatory markers. Serum levels of d- Dimer, procalcitonin, and ferritin correlated with COVID-19 mortality. Covid-19-affected patients can be prognosticated based on readily available and rapidly performed serum inflammatory marker assays and these are of specific relevance to resource-constrained environments like under-developed countries.

DECLARATIONS

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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