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Inflammatory mediator profile of hospitalised patients with COVID-19 during the second wave of the pandemic: A comparative study

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Abstract. Cough, fever and tiredness are upper respiratory symptoms of coronavirus disease 2019 (COVID-19). The emergence of the Delta variant, a significantly mutated and highly transmissible form of the severe acute respiratory syndrome coronavirus 2, initiated a fresh global wave of the COVID-19 pandemic. The timely and accurate clinical outcome prediction is vital for improving the management of patients with COVID-19 and identifying those who may be severely ill. In this retrospective observational study, a comparison of signs and symptoms and laboratory values was conducted between survivors and non-survivors of the second wave of COVID-19. Severe acute respiratory syndrome coronavirus 2-positive cases between June, 2021 and January, 2022 were confirmed using reverse transcriptase-polymerase chain reaction. Medical records were reviewed and collected until patient discharge/mortality. The levels of inflammatory biomarkers, symptoms and comorbidities of the patients were assessed. Analyses were performed using SPSS version 20.0. Of the 200 patients with COVID-19, 112 were male and 88 were female. Non-survivors outnumbered survivors, with the most common symptoms being sputum production, coughing, and hemoptysis ($P \leq 0.01$). Chronic kidney disease and chronic obstructive pulmonary disease were the most common co-occurring conditions among the non-survivors. On the day of admission, interleukin (IL)-6 OR=1.003 (1.000-1.007), C-reactive protein OR=1.038 (1.016-1.059) and lactate dehydrogenase OR=1.004 (1.001-1.006) levels were measured; however, the most significant predictor of morality were the D-dimer levels OR=1.016 (1.002-1.059). Serum ferritin and D-dimer levels were considerably higher in non-survivors than in survivors, while IL-6, C-reactive protein and lactate dehydrogenase levels were significantly higher in survivors at the time of admission. On day 3 of admission, serum ferritin, D-dimer, and IL-6 levels were higher in non-survivors than in the survivors of COVID-19. The following factors continued to be significant predictors of mortality among COVID-19 patients with binary logistic regression: Age, sputum, haemoptysis, cough and chronic obstructive pulmonary disease. Logistic regression analysis revealed that chronic kidney disease was not statistically significant. Understanding the variations in inflammatory profiles is crucial for devising personalized treatment strategies and improving clinical outcomes in the ongoing battle against COVID-19.

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Introduction

The coronavirus disease 2019 (COVID-19) remains widespread worldwide. The majority of patients of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibit moderate illness and common symptoms, such as fever, cough and exhaustion. The most frequent and fatal consequence of COVID-19 is pneumonia, which is still a respiratory illness. In patients with COVID-19, an increase in the levels of both pro- and anti-inflammatory markers has been observed. The most prevalent clinical manifestations of COVID-19 are fever and cough, which often progress to lower respiratory tract disease with poor clinical outcomes linked to advanced age and underlying medical problems (1,2). Since the emergence

of the novel coronavirus SARS-CoV-2 in 2019, scientists have examined the association between biological indicators and COVID-19 results. Within 6-8 h following the commencement of an acute viral or bacterial infection, the levels of the acute-phase reactant C-reactive protein (CRP), which is released by the liver in response to cytokines, such as interleukin (IL)-6, increases (3,4). The severity of COVID-19 has been predicted using CRP levels (5,6). Additionally, COVID-19 hyperinflammatory syndrome and the ensuing cytokine storm are associated with CRP levels >10 mg/dl, which may indicate severe consequences (7). The Alpha, Delta and Omicron variants vary. During this particular period, each variation of the COVID-19 virus was contagious. Certain variations were linked to increased mortality rates, whereas others exhibited a greater rate of dissemination in comparison to the remaining variants (8). Of note, the levels of three significant inflammatory markers, namely the platelet/lymphocyte ratio and CRP, were discovered to be higher in patients with COVID-19 than in participants who were COVID-19-negative. CRP is a common inflammatory marker whose levels are increased in various viral and inflammatory disorders. In a trial with 781 patients with COVID-19, obese patients had higher baseline and maximum CRP levels than non-obese patients; patients were twice as likely to succumb to the disease or need to be admitted to the intensive care unit (ICU) for every standard deviation increase in CRP level (9).

Mortality may be predicted using the levels of D-dimer and additional inflammatory markers, such as procalcitonin, CRP and IL-6. Fibrinolysis is indicated by an increase in the levels of D-dimer, a fibrin degradation product, during thrombotic episodes. Laboratory parameter predictors of mortality are significant as they can provide valuable insight into probable illness progression, processes and treatment approaches (10,11). Thrombosis is a well-known complication that significantly increases the risk of fatal consequences. Patients with COVID-19 exhibit significant alterations in the levels of coagulation markers. Patients who require ICU admission have been shown to have higher D-dimer levels than those who do not (12-14). The main cause of mortality in patients critically ill with COVID-19 has been reported to be coagulopathy, leading to disseminated intravascular coagulation and venous thromboembolism, which is one of the severe consequences observed in these patients. When patients with COVID-19 have systemic inflammatory response syndrome, the coagulation cascade is activated, which can lead to elevated levels of D-dimer (1,15). Zhou *et al* (15) found an association between high levels of D-dimer and disease severity in 129 hospitalised patients at the Shanghai Public Health Clinical Centre.

The hallmark of COVID-19 pathophysiology is known as the 'cytokine storm', which is defined by elevated levels of inflammatory markers, including IL-1 and IL-6 that stimulate platelets, endothelium, monocytes and the tissue factor VIIa pathway, thus causing thrombosis (15). SARS-CoV-2 infection causes comparable complex systemic inflammatory responses that release pro-inflammatory cytokines with various pleiotropic effects, such as the activation of the coagulation cascade, which interacts with coagulopathies to create a vicious cycle that is directly associated with a poor prognosis (13). Several other organ damage mechanisms are also induced by excessive IL-6 signalling, including T-cell maturation, vascular endothelial growth factor production, increased vascular permeability and decreased myocardial contractility (16,17). In late 2020, the first variants to raise concern, Alpha and Beta, surfaced with numerous mutations in the spike protein. The Delta variation gained worldwide dominance in 2021, and Omicron lineages with significant changes in the spike protein's receptor-binding region, such as BA.1 and BA.5, then emerged. The error-prone RNA polymerase of SARS-56 CoV-2, which results in ~1-2 mutations each month due to a lack of proofreading ability, facilitates viral evolution (18,19). The present study aimed to determine the potential biochemical determinants of the in-hospital mortality of patients with COVID-19.

Patients and methods

Study design, setting and participants. The present retrospective hospital-based study was conducted at the Chest Disease Hospital, Srinagar, Kashmir, India. The hospital was converted to a COVID-19 referral facility at the onset of the pandemic. The present study was conducted during the second wave of COVID-19 from June, 2021 to January, 2022. A total of 273 patients with COVID-19 were hospitalised. Patients >18 years of age were included in the study. The study protocol was approved by the Institutional Review Board of the Government Medical College (reference no. 1012/ETH/GMC). In front of impartial witnesses, written informed consent was provided by all patients admitted to wards other than the ICU, as well as by the guardians or families of patients admitted to the ICU. Nasopharyngeal swabs from individuals considered to have COVID-19 were obtained immediately and sent to the microbiology laboratory following the standard technique of viral transport. The laboratory-verified patients who were COVID-19-positive were included in the study, and from each patient confirmed to be positive for COVID-19, a 5-ml venous blood sample was obtained within 24 h of admission and on day 3 to assess the levels of inflammatory mediators.

A standardised data collection form was used to obtain the electronic medical records of the admitted patients. Data from patients with COVID-19 were included, along with laboratory results, comorbidities and demographic traits. The inclusion criteria were patients with severe pneumonia with a positive COVID-19 test. The exclusion criteria were patients with mild pneumonia and individuals whose data were incomplete, and patients who were hospitalised in the ICU for reasons other than COVID-19.

Statistical analysis. SPSS for Windows (version 20.0; IBM Corp.) was used to analyse the data. Of note, two junior residents crosschecked the data at the hospital before entering. Categorical variables are expressed as frequencies and percentages. Fisher's exact test, the Chi-squared test and odds ratios with 95% confidence intervals were calculated to assess the association between categorical variables and outcomes. The Mann-Whitney U test was used to compare biochemical parameters. Variables that exhibited significant associations in the univariate and binary analyses were subjected to regression analysis. A value of $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Baseline characteristics of the survivors and non-survivors of COVID-19.

Variable	Study population (n=200)	Survivors (124)	Non-survivors (n=76)	Odds ratio (95% CI)	P-value
Age (years)	60.96±13.7	58.29±14.2	65.3±11.8	NA	0.02
Sex					
Males	112 (56.0)	67 (54.03)	45 (59.21)	0.81 (0.45-1.44)	0.55
Females	88 (44.0)	57 (49.96)	31 (40.78)		
Symptoms					
Sputum	65 (32.5)	18 (14.52)	47 (61.84)	9.54 (4.83-18.85)	<0.01
Sore throat	82 (41)	6 (4.84)	76 (100.00)	NA	<0.01
Fever	199 (99.5)	124 (100)	75 (98.68)	NA	0.38
Anorexia	1 (0.5)	1 (0.81)	0 (0.00)	NA	<0.01[a]
Rhinitis	0 (0.00)	0 (0.00)	0 (0.00)	NA	0.999[a]
Anosmia	76 (38)	0 (0.00)	76 (100.00)	NA	<0.01
Haemoptysis	35 (17.5)	10 (8.1)	25 (32.89)	5.58 (2.50-12.49)	<0.01
Nausea	0 (0.00)	0 (0.00)	0 (0.00)	NA	0.999[a]
Fatigue	80 (40)	4 (3.22)	76 (100.00)	NA	<0.001
Headache	28 (14)	0 (0.00)	28 (36.84)	NA	<0.001
SOB	20 (100)	124 (100)	76 (100.00)	NA	0.999
Pulse rate	90.59±12.13	88.95±11.17	93.26±13.19	NA	<0.01
Respiratory rate	21.58±4.21	22.016±3.93	20.88±4.58	NA	0.06
Cough	91 (45.5)	29 (23.39)	62 (81.58)	14.50 (7.10-29.61)	<0.01
Comorbidity					
COPD	46 (23)	22 (17.74)	24 (31.58)	2.13 (1.09-4.17)	0.002
Asthma	37 (18.5)	19 (15.32)	18 (23.68)	1.71 (0.83-3.52)	0.18
DM	76 (38)	57 (45.97)	19 (25)	0.39 (0.20-0.73)	<0.01
CAD	19 (9.5)	14 (11.29)	5 (6.58)	0.55 (0.19-1.60)	0.26
CKD	19 (9.5)	3 (2.42)	16 (21.05)	10.75 (3.01-38.35)	<0.01
Cancer	8 (4)	2 (1.61)	6 (7.89)	0.19 (.037-.97)	0.05[a]
Hypertension	178 (89)	102 (82.26)	76 (100.00)	NA	<0.01
CLD	21 (10.5)	0 (0.00)	21 (27.63)	NA	<0.01[a]
Cerebrovascular disease	4 (2)	4 (3.23)	0 (0.00)	NA	0.16[a]
Thyroid disease	1 (0.5)	0 (0.00)	1 (1.32)	NA	0.38[a]
HIV	13 (6.5)	0 (0.00)	13 (17.11)	NA	<0.01[a]
Steroid use	15 (7.5)	0 (0.00)	15 (19.74)	NA	<0.01[a]
OSA	9 (4.5)	0 (0.00)	9 (11.84)	NA	<0.01[a]
Smoker	200 (100)	124 (100)	76 (100.00)	NA	NA

[a]Data were analysed using Fisher's exact test; the remaining variables were analysed using the Chi-squared test. SOB, shortness of breath; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CAD, coronary artery disease; CKD, chronic kidney disease; CLD, chronic liver disease; HIV, human immunodeficiency virus; OSA, obstructive sleep apnoea.

Results

A total of 200 patients confirmed to have COVID-19 were included in the present study; the number of males was 112 (56%) and that of females was 88 (44%), and the mean age of the study population was 60.96±13.7 years. The non-survivors (45 males and 31 females) were significantly older than the survivors (67 males and 57 females) (65.3±11.8 vs. 58.29±14.2 years; P=0.02). Sputum production [9.54 (4.83-18.85); P≤0.01], haemoptysis [5.58 (2.50-12.49); P≤0.01] and cough [14.50 (7.10-29.61); P≤0.01] were frequent symptoms observed among the non-survivors compared with the survivors. Among the comorbidities, chronic obstructive pulmonary disease (COPD) [2.13 (1.09-4.17); P=0.02] and chronic kidney disease (CKD) [10.75 (3.01-38.35); P≤0.01] were frequent among the non-survivors (Table I).

The D-dimer (mean rank, 158.14 vs. 65.17; P<0.001) and serum ferritin (mean rank, 102.03 vs. 98.74; P<0.001) levels were significantly higher among the deceased compared with the survivors of COVID-19, whereas the IL-6 (mean score, 111.03 vs. 77.59; P<0.05), CRP (mean score, 41.79 vs. 133.13; P<0.001] and lactate dehydrogenase (LDH) (mean score,

Table II. Comparison of age and inflammatory markers between survivors and non-survivors of COVID-19 upon admission.

Item	Outcome	Number	Mean rank	Sum of ranks	U[a]	P-value
Age	Non-survivors	76	118.91	9037.50	3312.5	<0.001
	Survivors	124	89.21	11062.50		
	Total	200				
IL-6	Non-survivors	76	77.59	5897.00	2971.0	<0.001
	Survivors	119	111.03	13213.00		
	Total	195				
D-dimer	Non-survivors	76	158.14	12018.50	331.5	<0.001
	Survivors	124	65.17	8081.50		
	Total	200				
CRP	Non-survivors	75	41.79	3134.00	284.0	<0.001
	Survivors	120	133.13	15976.00		
	Total	195				
Serum ferritin	Non-survivors	76	102.03	7754.50	4519.5	<0.001
	Survivors	123	98.74	12145.50		
	Total	199				
LDH	Non-survivors	76	79.70	6057.50	3131.5	<0.001
	Survivors	123	112.54	13842.50		
	Total	199				

[a]Data were analysed using the Mann-Whitney U test. IL, interleukin; CRP, C-reactive protein; LDH, lactate dehydrogenase.

112.54 vs. 79.70; P<0.001) levels were significantly higher among the survivors at the time of admission (Table II). On day 3 of admission, the IL-6 (mean score, 137.09 vs. 74.06; P<0.001), D-dimer (mean score, 150.42 vs. 69.90; P<0.05) and serum ferritin levels (mean score, 137.99 vs. 76.52; P<0.001) were higher among the deceased than among the survivors of COVID-19 (Table III).

The inflammatory markers that predicted mortality among patients with COVID-19 were IL-6 [1.003 (1.000-1.007)], CRP [1.038 (1.016-1.059)] and LDH [1.004 (1.001-1.006)] on the day of admission, while the D-dimer level [1.016 (1.002-1.059)] was the single most critical predictor of mortality on day 3 of admission (Table IV).

In the binary logistic regression analysis, it was found that age, sputum, haemoptysis, cough and COPD continued to be significant predictors of mortality among patients with COVID-19. CKD lost significance in the logistic regression. Cough [adjusted odds ratio (aOR)=11.31 (4.6-27.8); P=0.001], sputum (aOR=10.27 (3.99-26.43); P=0.001] and haemoptysis [aOR=5.47 (1.84-16.20); P=0.002] were strong symptom predictors of mortality. COPD [aOR=4.86 (1.72-13.71); P=0.003] was the only comorbidity (Table V).

Discussion

In the present study, symptoms such as haemoptysis, cough and sputum production were more common among non-survivors than in survivors. Among the comorbidities, COPD and CKD were common among the non-survivors. The study population had a mean age of 60.96±13.7 years. The non-survivors were considerably older than the survivors (65.3±11.8 vs. 58.29±14.2 years). It has been demonstrated that the male sex, hypertension, diabetes and cardiovascular disease are the main risk factors for mortality and severe illness due to COVID-19 (20,21). New insights into SARS-CoV-2 have led to the identification of various laboratory biomarkers that have been demonstrated to be associated with the severity of COVID-19 and have facilitated the prediction of treatment response (22,23).

In the present study, serum ferritin and D-dimer levels were considerably higher in the non-survivors than in the COVID-19 survivors, and on the 3rd day of admission, the D-dimer level was the only significant predictor of mortality [1.016 (1.002-1.059)]. D-dimer is a key biomarker with dual significance in haemostasis and inflammation and fibrin breakdown products have gained popularity. The breakdown of cross-linked fibrin, which is essential for haemostasis, produces D-dimers. In addition to its function as a fibrinolysis marker, D-dimer is a sensitive probe for persistent inflammation and thrombotic activity (24). When plasmin enzymatically cleaves fibrin during fibrinolysis D-dimer is produced. Increased fibrinolysis, which can occur in response to various stimuli, such as inflammation, thrombosis and tissue damage, causes elevated D-dimer levels in the blood. Interpreting the therapeutic consequences of D-dimer requires an understanding of its molecular origin. D-dimer has historically been used as a marker of hypercoagulability and fibrinolysis (24). In addition to its function in haemostasis, D-dimer also functions as an inflammatory mediator indicating an interaction between inflammation and coagulation. A number of inflammatory diseases, notably COVID-19, have been shown to be associated with elevated D-dimer levels (17,18,25,26). The precise pathways connecting inflammation to increased D-dimer levels, including interactions with immune cells and the endothelium,

Table III. Comparison of age and inflammatory markers between survivors and non-survivors of COVID-19 on day 3.

Item	Outcome	Number	Mean rank	Sum of ranks	U[a]	P-value
Age	Non-survivors	76	118.91	9037.50	3312.5	<0.001
	Survivors	124	89.21	11062.50		
	Total	200				
IL-6	Non-survivors	76	137.09	10419.00	1627.0	<0.001
	Survivors	120	74.06	8887.00		
	Total	196				
D-dimer	Non-survivors	76	150.42	11432.00	918.0	<0.001
	Survivors	124	69.90	8668.00		
	Total	200				
CRP	Non-survivors	76	50.37	3828.00	902.0	<0.001
	Survivors	121	129.55	15675.00		
	Total	197				
Serum ferritin	Non-survivors	76	137.99	10487.50	1786.5	<0.001
	Survivors	123	76.52	9412.50		
	Total	199				
LDH	Non-survivors	75	72.80	5460.00	2610.0	<0.001
	Survivors	124	116.45	14440.00		
	Total	199				

[a]Data were analysed using the Mann-Whitney U test. IL, interleukin; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table IV. Inflammatory predictors of mortality due to COVID-19.

							95% CI for Exp(B)	
Variables included	B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper
IL-6 day 1	0.003	0.002	4.248	1	0.039	1.003	1.000	1.007
IL-6 day 3	-0.005	0.002	6.422	1	0.011	0.995	0.991	0.999
D-dimer day 1	-0.026	0.009	9.242	1	0.002	0.974	0.958	0.991
D-dimer day 3	0.016	0.007	5.260	1	0.022	1.016	1.002	1.029
CRP day 1	0.037	0.011	12.250	1	0.01	1.038	1.016	1.059
CRP day 3	-0.025	0.017	2.067	1	0.151	0.976	0.944	1.009
Ferritin day 1	0.000	0.000	2.994	1	0.084	1.000	1.000	1.001
Ferritin day 3	-0.004	0.001	18.432	1	0.01	0.996	0.994	0.998
LDH day 1	0.004	0.001	8.389	1	0.004	1.004	1.001	1.006
LDH day 3	0.000	0.001	0.077	1	0.781	1.000	0.998	1.002
Hospital stay in days	0.031	0.041	0.569	1	0.451	1.031	0.952	1.117
Sex (male)	-0.539	0.609	0.783	1	0.376	0.583	0.177	1.924
Constant	0.542	0.970	0.312	1	0.576	1.719		

Multivariate regression analysis was performed to determine the inflammatory predictors of mortality due to COVID-19. IL, interleukin; CRP, C-reactive protein; LDH, lactate dehydrogenase; B, constant, df, degrees of freedom; SE, standard error; Sig., significance.

are intricate and multifaceted (23). According to the study by Klok *et al* (27), COVID-19 treatment in the facilities was related to D-dimer values >1 μg/ml, which were linked to an 18-fold increased risk of mortality. In patients with COVID-19, elevated D-dimer levels are linked to local pulmonary thrombosis, an immunohaemostatic reaction meant to stop and restrict viral transmission (28). Zhang *et al* (29) demonstrated that D-dimer levels >2 μg/ml at the time of admission may be taken into consideration as a predictor of mortality while a patient is in the hospital. However, the study by Soni *et al* (30) did not demonstrate that at the time of admission, the values of the same parameter >2 μg/ml predicted mortality.

In the present study, it was found that the levels of IL-6 [1.003 (1.0001.007)] were significantly higher among the

Table V. Socio-demographic, symptoms, and comorbidity predicators among survivors and non-survivors.

							95% CI for Exp(B)	
Variables included	B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper
Age	-0.049	0.017	8.126	1	0.004	0.952	0.920	0.985
Sputum	2.330	0.482	23.336	1	0.001	10.274	3.993	26.438
Haemoptysis	1.699	0.554	9.392	1	0.002	5.467	1.845	16.201
Cough	2.426	0.459	27.932	1	0.001	11.313	4.601	27.815
COPD	1.581	0.529	8.920	1	0.003	4.860	1.722	13.715
CKD	0.883	0.878	1.012	1	0.314	2.418	0.433	13.511
Constant	-2.481	1.492	2.766	1	0.096	0.084		

Binary regression analysis was performed to determine the inflammatory predictors of mortality due to COVID-19. IL, interleukin; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; B, constant; df, degrees of freedom; SE, standard error; Sig., significance.

survivors at admission and on day 3. Previous studies have shown that high serum concentrations of IL-6 are the main markers of the cytokine storm in patients SARS-CoV-2 positive (31,32). IL-6 is essential in inflammation, the immune system and a number of other physiological functions. After being discovered to be a B-cell differentiation factor at first, IL-6 is now known to be a pleiotropic cytokine that affects tissue homeostasis, inflammation and the immune system (31). In response to diverse stimuli, including infection, damage, or stress, fibroblasts, immunological cells and endothelial cells are among the cell types that release IL-6. Gp130 and IL-6 receptor are two components of the intricate receptor system that cytokines use to communicate. The potential of cytokines as therapeutic targets for autoimmune illnesses is underscored by their role in immune response dysregulation and enhanced autoantibody production (32). A previous study demonstrated that SARS-CoV-2 infection induces similar complex systemic inflammatory responses and releases pro-inflammatory cytokines that have a range of pleiotropic effects, including the activation of the coagulation cascade, which, when combined with coagulopathies, creates a vicious cycle that is strongly linked to a poor prognosis of patients (26).

In the present study, upon admission, CRP [1.038 (1.016-1.059)] and LDH [1.004 (1.001-1.006)] were the biomarkers that indicated the likelihood of mortality in patients with COVID-19. CRP is a critical indicator of COVID-19 inflammation. In patients with severe illness due to COVID-19, the CRP level is a much stronger predictor of mortality than age and platelet count (32). CRP, a well-known acute-phase reactant, is a key inflammatory mediator that affects several physiological and pathological states. One of the most well-known indicators of inflammation and tissue damage is CRP, a protein generated by the liver. IL-6, in particular, a pro-inflammatory cytokine involved in the acute-phase response, stimulates its creation (33-35). CRP is a useful biomarker for COVID-19 as elevated levels in the blood are suggestive of a continuing inflammatory process. Viral infections, traumatic injuries and persistent inflammatory diseases are among the stimuli that strongly control the hepatic production of CRP (36). The primary cause of elevated CRP synthesis is IL-6, which ultimately increases CRP transcription and translation by activating signalling pathways, such as the Janus kinase-signal transducer and activator of the transcription pathway. CRP synthesis can be used as a biomarker for tracking inflammatory conditions by understanding the regulatory processes underlying CRP production. CRP can recognise and attach to infections, injured cells, and foreign particles and is essential for the innate immune response. This contact facilitates the removal of these substances by initiating complement cascades. CRP is commonly acknowledged as a useful clinical biomarker (35). Increased serum levels of CRP are useful early markers of inflammation that can aid in the diagnosis and tracking of COVID-19. The present study demonstrated an association between a greater illness severity and elevated ferritin, CRP and D-dimer levels. This is consistent with the findings of other studies that found that a high concentration of inflammatory cytokines was linked to severe illness due to COVID-19 (25,37-40). Demirkol *et al* (41) reported that age had a strong positive correlation ($r=0.32$, $P<0.001$) with the CRP-to-lymphocyte ratio (CLR). In the present study, the CRP level and lymphocyte count, as CLR, were associated with worse outcomes in patients with COVID-19. In another study, high CRP levels and low lymphocyte counts were identified in individuals with heart failure, indicating a higher CLR (42).

The findings of the present retrospective clinical study may improve the understanding of the inflammatory mediator profile of patients with COVID-19. Certain inflammatory indicators, including IL-6 and CRP, have been linked to severe illness and poor outcomes. Monitoring these markers may help identify individuals who are at higher risk of developing severe disease, allowing for early intervention and appropriate resource allocation. Thus, the inflammatory response to COVID-19 may differ among patients. Individual inflammatory mediator profiles enable clinicians to adjust therapeutic regimens according to the immunological status and disease trajectory of each patient.

The presents study had certain limitations which should be mentioned: Compared with prospective studies, a retrospective design provides less control over the variables. Owing to the absence of controls, it can be difficult to account for potential confounders or isolate the impact of specific factors on inflammatory mediator profiles. The completeness and reliability of

medical records determine the quality and accuracy of data in retrospective studies. Documentation or coding errors may cause inconsistencies in inflammatory mediator profile analysis and interpretation.

In conclusion, in response to COVID 19 infection inflammatory markers IL-6, D-dimer and CRP have prognostic and therapeutic significance.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NNS, BAT and BSA were involved in the conceptualisation of the study, as well as in the study methodology, formal analysis, and in the writing, reviewing and editing of the manuscript. WUDG, AB, MN, NFD and SSF were involved in the study methodology, formal analysis, and in the writing of the original draft of the manuscript. SUAR, BSA and AB were involved in the study methodology and formal analysis. AB, BAT and SSF were involved in the writing, reviewing and editing of the manuscript. BAT and NNS were involved in the conceptualisation of the study, in the study methodology and in the provision of resources. SQK, SSF, MN, SUAR and BSA was involved in the formal analysis. WUDG, NNS, AB and BAT involved in the conceptualisation of the study, as well as in study supervision, funding acquisition, and in the writing, reviewing and editing of the manuscript. WUDG, NFD and NNS confirm the authenticity of all the raw data All authors have read and approved the final manuscript for publication.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Government Medical College, Srinagar, India, under protocol no. 1012/ETH/GMC. In front of impartial witnesses, written informed consent was provided by all patients admitted to wards other than the ICU as well as by the guardians or families of patients admitted to the ICU.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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