Clinical characteristics among patients with COVID-19: A single-center retrospective study

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Abstract. The aim of the present study was to investigate the clinical features and laboratory parameters of hospitalized patients with coronavirus disease 2019 (COVID-19) and assess the characteristics between severe and non-severe cases. The study retrospectively analyzed the clinical data of 1,096 patients, of which, 626 (57.11%) and 470 (42.89%) were categorized into severe and non-severe groups, respectively. Clinical parameters such as signs and symptoms, comorbidities, levels of D-dimer, C-reactive protein (CRP), interleukin 6 (IL-6) and lactate dehydrogenase were analyzed. The data are presented as frequencies, means and standard deviations. The chi-square test and Mann-Whitney U test were used to assess any significant differences between the severe and non-severe COVID-19 groups. The clinical symptoms in severe COVID-19 cases included anosmia ($P \leq 0.01$), sore throat ($P \leq 0.01$), fatigue ($P \leq 0.01$), headache ($P \leq 0.01$), and shortness of breath ($P \leq 0.01$). Laboratory findings showed a significant increase in CRP (21.90 ± 40.23 vs. 16.13 ± 21.82; $P \leq 0.01$) and IL-6 levels (58.92 ± 55.07 vs. 41.41 ± 38.30; $P \leq 0.01$). Patients with severe COVID-19 had significant lymphopenia compared with that in non-severe cases. Among the comorbidities, hypertension ($P \leq 0.01$) was significantly more frequent in patients with severe COVID-19. In conclusion, major derangements in laboratory parameters were observed in patients with severe COVID-19 infection.

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Introduction

Coronaviruses are enveloped, positive-sense RNA viruses that cause diseases ranging from the common cold to severe respiratory infections (1). Two betacoronaviruses are responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (2,3). An outbreak of pneumonia occurred in Wuhan City, China in January 2020. The causative agent of this unknown disease was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses, and the disease was termed coronavirus disease 2019 (COVID-19) (4-6). The disease became a pandemic and destabilized the global economy (7,8). As of March 27, 2022, the number of cumulative COVID-19 cases and deaths surpassed 479 million and 6 million, respectively. During the same period, India reported cumulative COVID-19 cases and deaths of 43 million and 524,000, respectively (9). The incubation period of the virus is 7-12 days, but in some cases it may be as long as 27 days (10). Viral replication occurs in the respiratory and gastrointestinal (GI) tract (11). Reports on the clinical features of patients with COVID-19 have shown significant differences in different regions. The most common symptoms in patients presenting with mild-to-moderate COVID-19 are headache, myalgia, fatigue, cough, mild dyspnea, and sore throat; other symptoms may include vomiting and diarrhea (12,13). SARS CoV and MERS outbreaks commonly present with fever and cough, leading to lower respiratory diseases with poor clinical outcomes (14). In COVID-19, hematological parameters, such as lymphocytopenia, leukocytosis, thrombocytopenia, leukopenia, lactate dehydrogenase (LDH), D-dimer, C-reactive protein (CRP), alanine transaminase (ALT), and aspartate aminotransferase (AST), are used for risk stratification (15). Previous studies have

reported fever, cough, headache, and muscle pain or fatigue as the most frequent symptoms of COVID-19 (16,17). Patients with comorbidities, such as diabetes, renal failure, cardiovascular diseases, and immunodeficiency, are more susceptible to COVID-19 (18,19). To mitigate COVID-19 complications, it is important to comprehensively evaluate underlying diseases in infected patients. In this context, the present study aimed to compare the demographic, laboratory, and clinical features of severe and non-severe COVID-19 infections to enhance case management.

Materials and methods

Study design, setting, and participants. The present retrospective hospital-based study was conducted at the referral Chest Disease Hospital of the Division of Kashmir (Srinagar, India), which is part of Jammu and Kashmir, a union territory of India. This hospital was converted to a COVID-19 referral hospital at the beginning of the pandemic. The study was conducted between May 2020 and May 2021. A total of 1,096 patients with COVID-19 were admitted. Patients >18 years of age were included in the study. The Institutional Review Board of the Chest Disease Hospital, Kashmir Division, approved the study protocol (reference no. 1012/ETH/GMC dated 16/6/2020). The procedures involved were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and the 2013 revised Declaration of Helsinki. Written informed consent was obtained from all patients admitted to non-ICU wards and from the guardians/relatives of patients admitted to the ICU in the presence of independent witnesses.

Inclusion and exclusion criteria. Patients with the following conditions were included in the study and divided into two groups: i) Severe COVID-19 infection: This group comprised patients with severe pneumonia and fever, respiratory rate >30 breaths/min, severe respiratory distress, or SpO_2 <90% on room air. Patients with acute respiratory distress syndrome (ARDS), sepsis, or septic shock were also included in this group (9). ii) Non-severe COVID-19 infection: This group comprised patients with COVID-19 but without pneumonia and severe respiratory distress or SpO_2 <95% (9) (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2). Patients with COVID-19 co-infected with other bacterial, fungal, or viral infections were excluded from the study.

Data extraction. The electronic medical records of the admitted patients were obtained using a standardized data collection form. The data included demographic characteristics, clinical manifestations, comorbidities, and laboratory findings of patients with non-severe and severe COVID-19.

Procedures. Nasopharyngeal swab from patients suspected with COVID-19 were collected under the standard procedure in viral transport medium and immediately transferred to the Biosafety Level-III laboratory of the Chest Disease Hospital. The samples were processed within 2 h, and RNA was extracted using an automated RNA extraction Genolution Nextractor NX-48S (Genolution, Inc.) according to the manufacturer's protocol. The single-step real-time reverse transcription-polymerase chain reaction (RT-PCR) assay was performed to confirm COVID-19. The thermal cycler setup for RT-PCR was 50˚C for 10 min and 95˚C for 10 min, followed by 40 cycles of denaturation at 94˚C for 15 sec and a fluorescence signal at 60˚C for 1 min. A cycle threshold value of >12 to <35 was marked as positive.

Statistical analysis. The data were analyzed with SPSS version 20.0 for Windows (IBM Corp.). Two senior doctors at the hospital crosschecked the data upon entry. Categorical variables were expressed as frequencies and percentages; normally distributed continuous variables were expressed as the mean ± standard deviation and medians with interquartile range (IQR) for non-random data. The Shapiro-Wilk test was used to determine the normality of the data. The proportions of categorical variables were compared using the chi-square test. Continuous data were randomly distributed using the independent t-test or Mann-Whitney U test. P<0.05 was considered to indicate a statistically significant difference.

Results

Demographics and clinical symptomology. A total of 1,096 patients with COVID-19 were hospitalized during the study period. Of these, 470 (42.8%) and 626 (57.1%) were categorized into non-severe and severe COVID-19 groups, respectively. The age range of patients in the study was 20-85 years and the median age was higher (49.89 years, IQR 41-58) among severe COVID-19 cases than that in non-severe cases (48.18 years, IQR 41-55). The majority of the studied clinical symptoms, except for anorexia and malaise, were significantly (P<0.05) increased among severe COVID-19 cases. The most frequent symptoms in severe COVID-19 cases were fever (97.8%), shortness of breath (99.2%), anosmia (96.1%), and malaise (85.4%) and in non-severe COVID-19 cases they were fever (97.7%), shortness of breath (89.3%), and malaise (82.7%) which were more common than sore throat or rhinitis. Furthermore, a significant number of deaths was observed in severe COVID-19 cases than that in non-severe cases (P<0.01; Table I).

Comorbidities. Hypertension was frequently observed in severe cases (94.4%) compared with that in non-severe cases (62.5%), while asthma (20.0%) was significantly higher in non-severe COVID-19 cases (Table II).

Laboratory findings. White blood cell, platelet, and lymphocyte counts were significantly (P<0.01) lower in severe COVID-19 cases (Table III). ALT levels were significantly higher (P<0.05) in non-severe COVID-19 cases. LDH, IL-6, and CRP levels were significantly higher (P<0.05) in severe COVID-19 cases than those in non-severe cases. In addition, serum ferritin levels were significantly lower (P<0.05) in severe COVID-19 cases than in non-severe cases (Table III).

Discussion

COVID-19 is a global health threat. Understanding the clinical features and laboratory derangements, particularly of severe cases, is key to the diagnosis and management of this disease.

Table I. Baseline characteristics, clinical symptoms and outcome of patients with severe and non-severe COVID-19 (n=1,096).

Parameters	Severe (n=626)	Non-severe (n=470)	P-value
A, Demographics			
Age (median (IQR))	49.89 (41.0-58.0)	48.18 (41.0-55.0)	0.96
Male	422 (67.4 %)	306 (65.1%)	
Female	201 (32.1%)	163 (34.6%)	0.40
B, Clinical symptoms			
Shortness of breath	621 (99.2%)	420 (89.3%)	<0.01
Fever	612 (97.76%)	459 (97.65%)	0.53
Anosmia	602 (96.1%)	253 (53.8%)	<0.01
Malaise	535 (85.4%)	389 (82.7%)	0.22
Fatigue	372 (59.4%)	162 (34.4%)	<0.01
Congestion	295 (47.1%)	116 (24.6%)	<0.01
Sore throat	286 (45.6%)	122 (25.9%)	<0.01
Anorexia	265 (42.3%)	186 (39.5%)	0.35
Headache	258 (41.2%)	27 (5.7%)	<0.01
Diarrhea	247 (39.4%)	78 (16.5%)	<0.01
Sputum	234 (37.4%)	81 (17.2%)	<0.01
Rhinitis	181 (28.9%)	0 (0%)	<0.01
Nausea	37 (5.9%)	81 (17.2%)	<0.01
C, Outcome			
Deaths	164 (26.1%)	15 (3.1%)	<0.01

IQR data, determined using the Chi-square test, is presented as the number of patients (%). COVID-19, coronavirus disease 2019; IQR, interquartile range.

Table II. Comorbidities of patients with severe and non-severe COVID-19 (n=1,096).

Parameters	Severe (n=626)	Non-severe (n=470)	P-value
Hypertension	591 (94.4%)	294 (62.5%)	<0.01
Diabetes	188 (30.0%)	177 (37.6%)	0.08
Obstructive sleep apnea	65 (10.3%)	50 (10.6%)	0.89
Chronic obstructive pulmonary disease	45 (7.1%)	39 (8.2%)	0.40
Coronary artery disease	17 (2.7%)	29 (6.1%)	0.05
Cardiovascular disease	10 (1.5%)	11 (2.34%)	0.37
Asthma	10 (1.59)	94 (20%)	<0.01
Chronic kidney disease	6 (0.95%)	4 (0.85)	0.05

Data, determined using the Chi-square test, is presented as the number of patients (%). COVID-19, coronavirus disease 2019.

A large sample study of 1,096 patients infected with COVID-19 admitted to the Chest Disease Hospital was conducted and the clinical manifestations, laboratory characteristics, and outcomes of severe and non-severe COVID-19 cases were compared. The results revealed that the clinical symptoms of fever, shortness of breath, and sore throat were present at the onset of the illness in both severe and non-severe cases. Sputum production in patients with COVID-19 is rarely observed (<1%) and is an important indicator for differentiating between viral and bacterial pneumonia. Sputum production in severe

Table III. Laboratory findings of 1,096 patients with severe and non-severe COVID-19.

Parameters	Severe (n=626)	Non-severe (n=470)	P-value
White blood cells			
<10000/μl	423 (67.5%)	289 (61.5%)	<0.01[a]
>10000/μl	203 (32.5%)	181 (38.5%)	
Platelet count			
<450x10^3/μl	293 (46.8%)	207 (44.0%)	<0.01[a]
>450x10^3/μl	333 (53.2%)	263 (56%)	
Lymphocyte count			
<4800/μl	345 (55.1%)	276 (58.7%)	<0.01[a]
>4800/μl	281(44.9%)	194 (41.3%)	
Aspartate aminotransferase (5-44 U/l)			
Mean ± SD	68.20±54.41	70.69±69.76	0.08[b]
Median	52.0	51.0	
Alanine aminotransferase (7-55 U/l)			
Mean ± SD	59.60±40.19	66.28±39.61	<0.01[b]
Median	48.0	59.0	
Alkaline phosphatase (40-129 U/l)			
Mean ± SD	124.68±64.68	131.48±90.05	0.77[b]
Median	108.0	101.0	
Lactate dehydrogenase (140-280 U/l)			
Mean ± SD	414.79±172.86	323.58±144.85	<0.01[b]
Median	347.0	299.0	
IL-6 (0-16 pg/ml)			
Mean ± SD	58.92±55.07	41.41±38.30	<0.01[b]
Median	37.0	31.0	
D-dimer (<0.5 mg/l)			
Mean ± SD	3.15±32.73	1.87±4.26	0.50[b]
Median	1.33	1.05	
C-reactive protein (<3 mg/l)			
Mean ± SD	21.90±40.23	16.13±21.82	<0.01[b]
Median	14.4	9.5	
Creatine phosphokinase (10-120 mcg/l)			
Mean ± SD	105.55±34.75	108.22±40.65	0.24[b]
Median	115.0	115.0	
Ferritin (20-250 ng/ml)			
Mean ± SD	188.87±46.01	230.87±47.90	<0.01[b]
Median	188.0	234.0	

[a]Chi-square test, significant at P<0.05. [b]Mann-Whitney U test, data is presented as the mean ± SD. COVID-19, coronavirus disease 2019.

cases is often caused by secondary bacterial infection (20,21). Diarrhea was more frequently observed in severe COVID-19 cases than in non-severe cases while nausea was more frequent in non-severe cases as compared to severe cases. The present study suggests that GI symptoms are crucial for the early diagnosis of COVID-19. The clinical symptoms of COVID-19 mimic SARS and MERS, except for anosmia (22). Herein, the fatality rates were 26.1 and 3.1% in the severe and non-severe cases, respectively. Older age was revealed to be associated with a greater risk of developing ARDS, and a poor immune response caused a higher mortality rate of 22% (23). Notably, the WHO reported a mortality rate of 9.6% for SARS CoV and 35% for MERS (24,25). In the present study, lymphopenia was significantly higher in severe cases than that in non-severe cases (P<0.01). A decrease in lymphocyte count in COVID-19 is a predictor of disease severity (26). Lymphopenia is a key factor that aids in the identification of severe infections caused by SARS-CoV-2, MERS-CoV, SARS-CoV, and other respiratory viruses, in addition to aiding in understanding disease pathogeneses, and provides a key to the management of COVID-19 with other coexisting diseases such as diabetes and hypertension (27). Proinflammatory cytokines have been demonstrated

to be associated with lymphopenia, and the cytokine storm may be a key factor in lymphopenia (20,28). Damage to the immune system caused by immunosenescence and COVID-19 leads to susceptibility to secondary infections such as bacterial pneumonia and mucormycosis (29). Previous studies have shown that lymphopenia is an indicator of clinical outcomes of COVID-19 (30). In the present study, elevated LDH (U/l) was observed in patients with severe COVID-19 (414.79±172.86 vs. 323.58±144.85; P<0.01). LDH is an enzyme that is found in various cell types. It catalyzes the inter-conversion of pyruvate and lactate and is also a marker of cardiac injury (31). A pooled analysis carried out by Henry *et al* on nine different studies showed that LDH levels were significantly higher in patients with severe COVID-19 (31). In severe cases, LDH is released into circulation and acts as a predictor of poor outcomes in patients admitted to the hospital (32).

Elevated D-dimer levels cause higher mortality and poor prognosis in severe COVID-19 cases (33,34). Demelo-Rodriguez *et al* examined the link between D-dimer and deep vein thrombosis (DVT) in 156 patients with COVID-19 admitted in a non-intensive care unit (34). Another study revealed that the D-dimer level was associated with a higher risk of proximal DVT (35). In the present study, D-dimer levels were not significantly higher in patients with severe COVID-19 compared with patients with non-severe COVID-19.

The inflammatory marker IL-6 (pg/ml) was significantly higher in severe COVID-19 cases than in non-severe cases (58.92±55.07 vs. 41.41±38.30; P<0.01). It has been reported that elevated levels of IL-6 promote thrombosis and cytokine storm, which is a hallmark of COVID-19 (36). Inflammatory cytokines induce pulmonary fibrinolysis, severe damage to alveoli, and endothelial apoptosis (37). Cytokine storms result from the release of proinflammatory cytokines and contribute to extensive lung damage. Cytokine production causes extensive damage to the entire human body. Patients with severe COVID-19 face hyperinflammation, known as 'cytokine release syndrome' (38). LDH and CRP levels are predictors of respiratory failure in COVID-19 and may be related to respiratory function (PaO_2/FiO_2) (39). Herein, a higher frequency of underlying medical conditions such as diabetes, hypertension, coronary artery disease, and asthma was observed in patients with severe COVID-19 than that in non-severe cases. The present study also suggests that patients with comorbidities are at a greater risk of developing severe COVID-19. Similar findings have been reported by Nikpouraghdam *et al* (27). CRP is an important inflammatory marker in COVID-19 (40). In the present study, elevated CRP levels were observed in the severe COVID-19 group than in the non-severe COVID-19 group; CRP levels >40 mg/l are an indicator of the progression of pneumonia and ARDS (41). In a previous study, significant differences in the levels of inflammatory markers, such as D-dimer, CRP, and IL-6, between severe and non-severe COVID-19 cases were noted, and lymphocytopenia and neutrophilia were prominent in patients with COVID-19 (42). Ferritin levels were revealed to be decreased in severe cases of COVID-19 and this may be attributed to a higher proportion of anemic patients in the study population. A study by Hilal and Mushtaq revealed a high prevalence of anemia in a geriatric population of Kashmir in both sexes; 812 out of 840 (96.67%) females and 738 out of 1,160 (63.62%) males were found to be anemic (43) and a recent study reported that in 50% of the COVID-19 cases, the ferritin levels were significantly low (44).

Limitations of the present study include the retrospective hospital-based design and non-reporting of secondary infections.

In conclusion, laboratory derangements, frequency of comorbidities, and deaths were more frequent among severe COVID-19 cases than among non-severe patients admitted to the Chest Disease Hospital in the Kashmir valley. The parameters assessed in the present study may help determine the severity of COVID-19 and initiate timely interventions that can lead to decreased morbidity and mortality.

Availability of data and materials

The data reported in the present study may be requested from the corresponding author.

Authors' contributions

AF, BAT and NNS conceived the study. AB and SQK contributed to data curation. AB, HM NNS and MN contributed to the analysis of the data. NNS and AB contributed to the methodology. NNS supervised the study. MSW, AF and HM contributed to the validation of the results. BAT, AB and SQK analyzed the data and wrote the original draft. NNS, MSW and AB wrote, reviewed and edited the manuscript. BAT and NNS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Institutional Review Board of the Chest Disease Hospital, Kashmir Division, approved the study protocol (reference no. 1012/ETH/GMC dated 16/6/2020). The procedures involved were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and the 2013 revised Declaration of Helsinki (1975). Written informed consent was obtained from all patients admitted to non-ICU wards and from the guardians/relatives of patients admitted to the ICU in the presence of independent witnesses.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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