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Clinical Characteristics and Prognostic Factors of Severity in Covid-19 Patients in Lahore, Pakistan

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Review Article

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Abstract

Background: The coronavirus disease outbreak of 2019 (COVID-19) has developed into a global emergency. COVID-19's severity is strongly correlated with its mortality rate. We aimed to examine the demographic, medical, laboratory, and imaging characteristics of 120 patients affected by COVID-19.

Methods: 120 COVID-19 infected- patients who tested positive from the throat swab specimen on quantitative reverse transcriptase-polymerase chain reaction (q RT-PCR) were included. Demographic, clinical, radiographic, and laboratory data were obtained and analyzed.

Results: Male gender, urban residence, current smoker, exposure history, sore-throat, dyspnoea, cough, headache, diarrhea, coronary heart disease, chronic obstructive lung disease, and cancer, decreased level of hemoglobin and albumin and increased level of lymphocyte count, leukocyte count, LDH level, D-dimer, serum ferritin, total bilirubin, urea level (p-value < 0.05) were contributing factors towards disease severity. In the binary logistic regression model LDH (OR 1.002, [CI, 1.001-1.003]; p = 0.001), and D-dimer (OR 1.377, [CI, 1.161-1.633]; p=0.001) were independent predictors of disease severity.

Conclusion: Appropriate evaluation of prognostic factors and provision of the appropriate interventions in high-risk patients can decrease the mortality associated with COVID-19.

Keywords: COVID-19; Severe Disease; Prognostic Factor; SARS-Cov-2 Detection

Introduction

A group of patients with unusual severe pneumonia was reported in Wuhan, China, in December 2019 about the Huanan Seafood Wholesale Market [1]. The World Health Organization (WHO) gave the name to the new virus as coronavirus disease 2019 (COVID-19) and it was responsible for acute respiratory distress syndrome (ARDS) as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. COVID-19 is a communicable disease both in the asymptomatic and symptomatic form with an accepted incubation period of about 14 days. A quick rise in cases and deaths in the starting months of 2020 made this disease the most serious health crisis in those times in the whole world [3].

About 2.28 million patients were identified to be affected with COVID-19 with 155,124 deaths up to April 19, 2020, across the whole world. However almost 81% of these

COVID-19 cases were mild, 14% were severe and 5% were in a critical situation. As far as critical patients are concerned the observed death rate was approximately 50.0% [4]. Many characteristics related to severe COVID-19 have been explored in China. Being elderly, male gender, presence of other diseases, low oxygen saturation, and abnormal lab results (high lactate dehydrogenase [LDH], high procalcitonin, low CD4 cell count, low albumin level) were found to be risk factors for severe COVID-19 [5-10].

After the uncertain outbreak of COVID-19 in Italy, China, and Spain on March 13, 2020, European-based risk assessment in COVID-19 patients in the ICU (RISC-19-ICU) record was introduced for permitting near-real-time assessment of the major medical factors of seriously ill patients during the developing COVID-19 outbreak. Anyhow, patient- and disease-associated characteristics change from area to area, and these characteristics can be related to the severity of COVID-19. No research related to prognostic factors for severe COVID-19 disease has been done in Lahore; Pakistan. The current study was done for the identification of prognostic factors related to severe disease in COVID-19 patients in Lahore, Pakistan. Understanding the patient features related to severe COVID-19 is vital not only for triage and therapeutic selection in critically ill patients but also for the generation of hypotheses grounded on the pathophysiology of the disease and for the provision of the design of more studies.

Methods

Study Design and Participants

The current study was retrospective observation research of 120 diagnosed COVID-19 patients at Lahore General Hospital, Lahore, Pakistan from 1 March to 30 July 2021. All adult male and female patients (age ≥18 years) having confirmed COVID-19 admitted in the hospital through outpatient department or emergency were included in the study. The need for informed consent was not there because of the retrospective design of the study.

Data Collection and Definitions

Demographic, epidemiological, clinical, laboratory, radiographic, and final data were taken from the medical records of the hospital by using a standardized data collection form. Demographic and clinical data include age, gender, residence, current smoking status, exposure history, co-morbidities, and symptoms on admission.

Laboratory data included complete blood count, coagulation profile, blood biochemistry (including Liver and renal function tests, Lactate dehydrogenase), and infection-related biomarkers (serum ferritin, C-reactive protein, and D-dimer) and outcome (Dead or discharge). Chest X-Ray was obtained for all patients and check for any consolidation, ground-glass opacities, and bilateral pulmonary infiltration. All data were collected and assessed by all authors and any differences in interpretation between the reviews were corrected.

Confirmed cases of COVID-19 were said to be those who tested positive from the throat swab specimen on quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR). The mild disease was defined as mild signs and symptoms and normal findings or absence of pneumonia on radiographic examination. The moderate disease was demarcated as symptoms related to respiratory tract and fever, along with pneumonia confirmed on radiographic assessment. Severe disease was described as shortness of breath, respiratory rate ≥30/minute, the oxygen level of blood ≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% in lung field within 24–48 h. Critically ill were said to be those having respiratory failure and requiring mechanical ventilation, or those with septic shock, and/or multiple organ dysfunction/failure and requiring ICU care and management [3,7].

Ethical Consideration

After the detailed explanation of the study purpose and procedures informed written consent were obtained from all the participants were obtained from the studies patient. The ethical permission was obtained from the ethical committee of hospital and King Edward Medical University, Lahore.

Statistical analysis

Data were entered and assessed by the use of SPSS software (ver. 24.0; SPSS Inc., Chicago, IL, USA). Categorical variables were explained as numbers and percentages and their comparison was done by the $\chi 2$ test or Fisher's exact test. Continuous data were expressed as means ± standard deviation and were compared by the analysis of variance or Kruskal-Wallis rank-sum test for comparison between multiple groups. Kolmogorov–Smirnov tests were carried out to assess the normality of data. The non-normality of data resulted in the use of nonparametric tests to assess the difference in mean ranks in different sociodemographic categories. Spearman correlation coefficient was used to explain the relationships among different variables and disease severity. The binary logistic regression model was employed for recognizing factors related to poor outcomes. Odds ratios and their associated 95% confidence intervals (CIs) were used as measures of effect size. A p-value less than 0.05 (two-tailed) were considered to be statistically significant.

Results

Demographic and Clinical Characteristics

In the current study, 120 diagnosed COVID-19 patients, admitted to the hospital were included. The patients were divided into four levels of severity (mild, moderate, severe, and critically ill) based on the criteria mentioned above.19 patients were recognized to have a mild level of severity (15.83%), 53 had moderate disease (44.16%), 35 had severe disease (29.16%), 13 were critically ill patients (10.83%). The patients having the severe or critical ill disease were (39.9%).

Table 1 of the study showed the socio-demographic and epidemiological characteristics of the patients at admission. The mean age of the patients was 50.19 ± 13.289. The characteristics showed that most patients were male (65.8%), from urban residence (87.5%), had a history of exposure (98.3%), were non-smoker (14.2%). The most common symptoms were fever (100.0%), chills (95.8%), and myalgia (90.0%) respectively. There was a statistically significant difference between gender, residence, current smoking status, exposure history, sore-throat, dyspnoea, cough, headache, and diarrhea and among the four groups of levels of severity ($p < 0.05$).

Characteristics	Mild disease (n=19)	Moderate disease (n=53)	Severe disease (n=35)	Critically ill (n=13)	Total (n=120)	p-value
Gender						
Male	10(52.6)	27(50.9)	29(82.9)	13(100.0)	79(65.8)	0.001
Female	9(47.4)	26(49.1)	6(17.1)	0(0.00)	41(34.2)	
Residence						
Urban	19(15.8)	45(37.5)	33(27.5)	8(6.7)	105(87.5)	0.006
Rural	0(0.00)	8(6.7)	2(1.7)	5(4.2)	15(12.5)	
Current smoker						
Yes	1(5.3)	4(7.5)	8(6.7)	4(3.3)	17(14.2)	0.041
No	18(94.7)	49(92.5)	27(77.1)	9(69.2)	103(85.8)	
Exposure history						
Yes	(17(89.5)	53(100.0)	35(100.0)	13(100.0)	118(98.3)	0.013
No	2(1.7)	0(0.00)	0(0.00)	0(0.00)	2(1.7)	
Symptoms, n (%)						
Fever	18(94.7)	53(100.0)	35(100.0)	13(100.0)	119(100.0)	0.147
Chills	18(94.7)	49(92.5)	35(100.0)	13(100.0)	115(95.8)	0.3
Myalgia	18(94.7)	49(92.5)	28(23.3)	13(100.0)	108(90.0)	0.104
Sore-throat	13(68.4)	10(18.9)	30(85.7)	13(100.0)	66(55.0)	0.001
Short of breath	16(84.2)	21(39.6)	23(65.7)	13(100.0)	73(60.8)	0.001
Cough	18(94.7)	46(86.8)	24(68.6)	13(100.0)	101(84.2)	0.013
Headache	8(42.1)	5(9.4)	22(62.9)	8(61.5)	43(35.8)	0.001
Diarrhoea	3(15.8)	6(11.3)	14(40.0)	8(61.5)	31(25.8)	0.001
Nausea/Vomiting	3(15.8)	12(22.6)	10(28.6)	0(0.00)	25(20.8)	0.165
Runny nose	4(21.1)	12(22.6)	7(20.0)	0(0.00)	23(19.2)	0.314
Dizziness	3(15.8)	10(18.9)	10(28.6)	0(0.00)	23(19.2)	0.156
Clinical outcomes						
Death	3(15.8)	3(5.7)	2(5.7)	1(7.7)	9(7.5)	0.512

Table 1: Demographic and epidemiologic characteristics of patients with COVID-19 in Lahore.

118 patients out of 120 had co-existing conditions such as hypertension (34.2%), diabetes mellitus (39.2%), coronary heart disease (12.5%), chronic kidney disease (2.5%), chronic obstructive lung disease (7.5%), liver disease (0.8%) and cancer (1.7%). There was a statistically significant difference between coronary heart disease, chronic obstructive lung disease, and cancer and among the four groups of levels of severity ($p < 0.05$) (Table 2).

Characteristics	Mild disease (n=19)	Moderate disease (n=53)	Severe disease (n=35)	Critically ill (n=13)	Total (n=120)	p-value
Hypertension	9(47.4)	14(26.4)	15(42.9)	3(23.1)	41(34.2)	0.189
Diabetes Mellitus	8(42.1)	18(34.0)	18(51.4)	3(23.1)	47(39.2)	0.232
Coronary Heart disease	5(26.3)	2(3.8)	5(14.3)	3(23.1)	15(12.5)	0.038
Chronic Kidney diseases	1(5.3)	0(0.00)	2(5.7)	0(0.00)	3(2.5)	0.287
Chronic Obstructive Lung disease	6(31.6)	3(5.7)	0(0.00)	0(0.00)	9(7.5)	0.001
Liver disease	1(5.3)	0(0.00)	0(0.00)	0(0.00)	1(0.8)	0.147
Cancer	2(10.5)	0(0.00)	0(0.00)	0(0.00)	2(1.7)	0.013

Table 2: Comorbidities of patients with COVID-19.

Laboratory and Radiographic Findings

Table 3 showed the laboratory findings of the patients at the admission. The 48 (40%) patients showed anemia, 45(37.5%) had thrombocytopenia, 4(3.33%) had lymphopenia and 3(2.5) patients had leucopenia on admission. Alanine aminotransferase (ALT) levels were elevated in 34 patients (28.3%), aspartate transaminase (AST) levels were raised in 62 patients (51.6%), alkaline phosphatase levels (ALP) were increased in 36 patients (30%), and lactate dehydrogenase (LDH) levels were raised in 90 patients (75%). The albumin level was reduced in 86 patients (71.6%). D-dimer levels were elevated in 118 patients (98.3%), C-reactive protein levels (CRP) were elevated in 68 patients (56.6%), Total bilirubin was elevated in 38 patients (31.6%), urea levels were increased in 110 patients (91.6%) and serum Creatinine levels were increased in 67 patients (55.8%). Serum ferritin levels were increased in 78 patients (65%) and international normalized ratio (INR) was increased in 95 patients (79.1%).

A Kruskal-Wallis test made evident that there was statistically important variation in hemoglobin level, lymphocyte count, leukocyte count, D-dimer, serum ferritin, total bilirubin, albumin level, urea level, and Creatinine level and between the four severity group ($p < 0.05$) (Table 3). Table 4 showed the radiographic characteristics in patients affected by COVID-19. 10 patients in the category of the mild disease had ground-glass opacities in lung fields (14.1%). 31 patients in the moderate group had consolidation (42.5%) and 24 patients in the severe group had consolidation (32.9%). 9 patients in the critical ill group had consolidation (12.3%), ground-glass opacities (16.9%), and bilateral pulmonary infiltration (27.7%) (Table 4).

Laboratory finding	Mild disease (n=19)	Moderate disease	Severe disease	Critically ill	Statistics	p-value
	Mean Rank	(n=53)	(n=35)	(n=13)	$\chi 2$ value	
		Mean Rank	Mean Rank	Mean Rank		
Hemoglobin level, g/L	50.29	60.53	74.79	35.85	13.575	**0.004**
Platelet count, × 10^9 per L	67.89	62.37	60.99	40.77	5.206	0.157
Lymphocyte count 10^9 cells/L	57.71	73.15	37.87	73.92	24.503	**0.001**
Leukocyte count, 10^9 cells/L	34.95	63.31	66.39	70.54	12.695	**0.005**
ALT level, U/L	60.66	58.1	61.7	66.81	0.722	0.868
AST level, U/L	58.37	62.52	57.8	62.65	0.515	0.916
ALP level, U/L	58.13	59.37	57.01	77.96	3.775	0.287

LDH level, U/L	50.39	60.51	62.71	69.27	2.573	0.462
D-dimer, mcg/mL	34.66	54.48	77.5	77.04	22.399	**0.001**
C-reactive protein level, mg/L	66.55	63	51.99	64.38	3.118	0.374
Serum ferritin ng/mL	46.71	53.15	74.13	73.92	12.664	**0.005**
Total bilirubin level, mg/dL	59.84	65.87	45.64	79.58	12.029	**0.007**
Albumin level, g/L	64.92	43.71	80.86	67.69	25.742	**0.001**
Urea level, mg/dL	49.97	54.62	59.84	101.62	21.462	**0.001**
Creatinine level mg/dL	51.55	50.61	66.91	96.62	20.928	**0.001**
Prothrombin time, s	55.08	56.99	63.03	75.92	3.829	0.281

Table 3: Laboratory findings in Patients with COVID-19 at admission.

Characteristics	Mild disease (n=19)	Moderate disease (n=53)	Severe disease (n=35)	Critically ill (n=13)
Consolidation	9(12.3)	31(42.5)	24(32.9)	9(12.3)
Ground-glass opacities	10(14.1)	28(39.4)	21(29.6)	12(16.9)
Bilateral pulmonary infiltration	2(4.3)	16(34.0)	16(34.0)	13(27.7)

Table 4: Radiographic features in patients with COVID-19.

According to the clinical outcome, patients were divided into two categories, those with adverse events and without an adverse event. Adverse events were explained as the presence of any one of the below mentioned: respiratory rates Q30 breaths per minute, PaO2/FiO2 R300 mmHg, peripheral oxygen saturation (SpO2) R93%, or admission to the intensive care unit. The category of patients with adverse events comprises patients with severe disease or the patients who are critically ill.

Prognostic Factors for Severe COVID-19

Table 5 showed relationships between socio-demographic, clinical features, and disease gravity by use of the spearmen correlation coefficient. Chronic obstructive lung disease, D-dimer, LDH level, serum ferritin, urea level, and Creatinine level expressed remarkable positive association with the gravity of the disease (p-value < 0.001). Gender, sore throat, headache, and diarrhea expressed a remarkable negative association with the disease gravity (p-value < 0.001).

Parameter	Spearman correlation coefficient	p-value
Gender	-0.353	0.001
Residence	0.176	0.076
Current smoking	-0.251	0.006
Exposure history	-0.202	0.027
Fever	-0.142	0.121
Chills	-0.139	0.13
Myalgia	0.084	0.364
Cough	0.121	0.188
Dysnopea	-0.137	0.135
Sore-throat	-0.401	0.001
Headache	-0.32	0.001
Diarrhoea	-0.352	0.001
Runny nose	0.11	0.231

Dizziness	0.001	0.992
Nausea/vomiting	0.019	0.835
Hypertension	0.029	0.75
Diabetes Mellitus	-0.014	0.88
Coronary Heart disease	-0.021	0.824
Chronic Kidney diseases	-0.014	0.88
Chronic Obstructive Lung disease	0.337	0.001
Liver disease	0.142	0.121
Cancer	0.202	0.027
Hemoglobin level, g/L	0.06	0.517
Platelet count, × 10^9 per L	-0.161	0.079
Lymphocyte count (%)	-0.158	0.085
Leukocyte count, 109 cells/L	0.262	0.004
ALT level, U/L	0.054	0.557
AST level, U/L	-0.006	0.949
ALP level, U/L	0.086	0.348
LDH level, U/L	0.625	0.001
D-dimer, mg/mL	0.51	0.001
C-reactive protein level, mg/L	-0.102	0.267
Serum ferritin	0.561	0.001
Total bilirubin level, mmol/L	-0.042	0.649
Albumin level, g/L	0.259	0.004
Urea level, mmol/L	0.314	0.001
Creatinine level, μmol/L	0.356	0.001
Prothrombin time, s	0.159	0.083
Age	0.092	0.315

Table 5: Correlation coefficient and p-value between clinical characteristics and disease severity.

The variables which showed a strong positive correlation (D-dimer, LDH level, serum ferritin) with disease severity were included in a binary logistic regression model to identify independent predictors of disease severity. The factors D-dimer and LDH were independents predictors of disease severity (Table 6). In the analysis, D-dimer, ferritin and LDH are defined as a continuous variable.

Parameter	Odds ratio	95% CI	p-value
LDH level, U/L	1.002	1.001-1.003	0.001
D-dimer, mg/mL	1.377	1.161-1.633	0.001
Serum ferritin	1	1.00-1.00	0.021

Table 6: Independent predictors of disease severity by multivariate binary logistic regression.

Discussion

The recognition of prognostic variables may help physicians in the evidence-based treatment of COVID-19. This present retrospective observational study analyzed the demographic, clinical, laboratory, and imaging features of 120 patients with COVID-19 in Lahore, Pakistan to determine potential biomarkers that may affect the prognosis and management of these patients. We showed that factors such as D-dimer and LDH were independents predictors of disease severity in hospitalized COVID-19 patients.

In the current study, socio-demographic and clinical characteristics who become ill due to COVID-19 were predominantly male, middle-aged, had exposure history, non-smoker, had fever chills, myalgia, and sore-throat

and with co-morbidities predominantly hypertension and diabetes mellitus. These findings are in line with previous study findings most of which had predominantly regional and national focus [3,11,12]. A particular reason for poor outcomes in these patients can be a defect in B-cell and T-cell response with age and a resultant deficient control of viral replication in the body and a prolonged and exaggerated pro-inflammatory response with excessive production of type-2 cytokines.

The patients who had comorbid conditions had an increased risk of developing severe disease on the assessment of inflammatory factors, hyper-coagulable state, and damage to organs. The present study showed that there is a statistically significant difference between coronary heart disease, chronic obstructive lung disease, and cancer and among the four groups of levels of severity ($p < 0.05$) [3,12,13]. According to Adam et al. the patient experiencing an acute exacerbation of COPD had an increased risk of failure of treatment and in-hospital mortality [14]. The reason for this poor outcome in these infectious diseases is 1) decreased neutrophil function; 2) diminished T cell response; 3) humoral immunity dysfunction, and 4) suppression of the antioxidant system [15].

Laboratory analysis at the time of admission demonstrated that statistically significant differences in hemoglobin level, lymphocyte count, leukocyte count, D-dimer, serum ferritin, total bilirubin, albumin level, urea level, and Creatinine level and between the four severity group ($p < 0.05$). Liver injury in patients with SARS-CoV-2 infection is not rare. It was found that 28.3% of the patients had raised ALT levels, 51.6% had raised AST levels, 30% had raised ALP levels and 90 patients (75%) had increased lactate dehydrogenase (LDH) levels. Moreover, AST levels were significantly higher in patients who were critically ill and albumin levels were found to be significantly lower in severely ill patients. These findings are consistent with the results of previous studies [3,11,12]. Upon recent literature review, it was observed that among the admitted COVID-19 patients, 46% had elevated AST, and 35% had elevated ALT with mildly elevated total bilirubin levels [16]. The mechanism underlying these pathological findings is considered to be multifactorial and is associated with micro-thrombotic endotheliosis, infection of hepatocytes with the covid-19 virus, deregulation of the immune system, and drug-induced injury to the liver [16].

We found that the inflammatory markers such as D-dimer, LDH level, and serum ferritin show a strong positive correlation to the disease severity (p-value < 0.001). These findings are in line with the previous findings [3,12]. The iron status of the body can affect the serum ferritin levels of the body and might indicate a hyper-immune state. It is also a marker of a known complication of viral infection hemophagocytic lymphohistiocytosis [3,11]. In multivariate binary logistic regression, increased level of D-dimer (OR, 1.377; 95% CI, 1.161-1.633; $p < 0.001$) was independent predictors of adverse event in hospitalized COVID-19 patients [11, 12]. Increased D-dimers levels were also associated with in-hospital mortality thus indicating that this marker can be used as a single user test to predict the outcome in patients admitted with COVID-19 [17,18]. There is still not much evidence about the exact causal mechanism of D-dimers levels and whether they are a result of a systemic inflammatory response or a specific effect of SARS-COV-2 infection. Deregulation of the coagulation and anticoagulation cascade can worsen lung damage in patients with COVID-19. The abnormal coagulation system including the cellular and protein components can be due attributed to viral replication and immune pathogenesis in influenza [17,18].

In multivariate binary logistic regression analysis, an increased level of LDH (OR, 1.002; 95% CI, 1.001-1.003; $p < 0.001$) was also an independent predictor of an adverse event in hospitalized COVID-19 patients. Several studies found an association between LDH and worse outcomes in a patient hospitalized with COVID [3,12,19,20]. In severe infections, cytokine-mediated lung damage can result in LDH release [19,20]. As the lung tissue has LDH (isozyme 3), the patients with severe COVID-19 infection are expected to release a great amount of LDH into the blood as severe interstitial pneumonia progressing to respiratory distress syndrome is a key feature of this disease [20].

Early clinical and laboratory factors contributing to disease severity were male gender, urban residence, current smoker, exposure history, sore-throat, dyspnoea, cough, headache, diarrhea, coronary heart disease, chronic obstructive lung disease, and cancer, decreased level of hemoglobin and albumin and increased level of lymphocyte count, leukocyte count, LDH level, D-dimer, serum ferritin, total bilirubin, albumin, urea level (p-value < 0.05). In the binary logistic regression model LDH (OR 1.002, [CI, 1.001-1.003]; $p = 0.001$), and D-dimer (OR 1.377, [CI, 1.161-1.633]; $p=0.001$) were independent predictors of disease severity. Serum ferritin did not reach statistical significance possibly due to its effect on other factors. The predictors of severe disease progression on Pakistani patients and those in Chinese patients were not much different.

This study has few strengths and limitations as well. This is the first-ever study in Lahore, Pakistan to provide a comprehensive estimate of the several prognostic factors among Covid-19 affected hospitalized patients. The information provided by this study highlights the importance of the recognition of predictive variables that may help physicians in the evidence-based treatment of COVID-19. First, this was a retrospective study conducted in a single center in Lahore, which subjected only hospitalized

patients. Therefore, these results cannot be generalized to all COVID-19 patients. Secondly, this study did not include the use of antiviral and corticosteroids as variables. Our focus was on the baseline clinical features and laboratory findings in worsening cases rather than the treatment of patients. Thirdly the selection bias could not be eliminated as the data used was not population-based. The severity of the disease can vary between the different hospitals in the same region. Fourthly, the pro-inflammatory cytokines and the early response by CD8 T cells which are also associated with disease severity were not taken into account in this study.

Conclusion

In conclusion, COVID-19 not only affects the lungs but also other body organs like the heart and the liver. The disease severity increases with advancing age. The results showed that the LDH and D-dimers levels are independent predictors of the severity of disease in COVID-19 patients admitted in Lahore Pakistan. The possibility of progression to severe disease increased with these increasing prognostic factors. The case fatality rate in COVID-19 patients can be decreased by careful monitoring of the prognostic factors and interventions at the appropriate time in high-risk patients.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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