

ORIGINAL ARTICLE

Predictors for Disease Severity in Covid-19RIDA GUL¹, AYESHA GUL AYESHA GUL², RIDA GUL³, HAMZA SATTAR KHAN⁴, DAWOOD KHAN⁵, MUHAMMAD HAROON⁶, ASGHAR KHAN⁷¹Trainee Medical Officer, Department of Medicine, Lady Reading Hospital, Peshawar²Registrar Critical Care Department, Bahria International Hospital, Islamabad³Trainee Medical Officer, Department of Medicine, Lady Reading Hospital, Peshawar⁴Speciality Registrar in Endocrinology & Diabetes, Aintree University Hospital, UK Acute Medicine Department, James Paget Hospital, UK⁵Trainee medical officer, Dermatology Department of Dermatology, Khyber Teaching Hospital, Peshawar⁶Medical Director Critical Care Department, Bahria International Hospital, Islamabad⁷Medical officer, Acute Medicine Department, Russel Hall Hospital Dudley, West Midlands UK

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ABSTRACT**Background:** Coronavirus disease 2019 affects millions of people to date. Age, comorbidities, fever, shortness of breath, and different Laboratory parameters like serum ferritin, C-reactive protein, and lactate dehydrogenase level are the important predictors for the severity of the disease.**Material and methods:** This case-control type study was conducted in April to June 2021 in Khyber Teaching Hospital Peshawar. PCR-detected coronavirus disease 2019 patients were assessed. These patients were divided into four groups based on presenting symptoms, image findings for pneumonia, oxygen saturation, and ventilatory support. These groups were compared for different parameters, including the presenting symptoms and laboratory parameters.**Results:** Out of 140 patients, 54.3% were males. There was a statistically significant difference ($p < 0.05$) in presenting complaints like fever, shortness of breath, body aches, loss of taste, anorexia, and laboratory parameters like serum ferritin, total leucocyte count, lactate dehydrogenase, C-reactive proteins, and d-dimers in these groups based on the severity of the disease. These parameters were independent predictors for disease severity in Coronavirus disease 2019. Further studies are recommended with a large sample size for more evaluation of these associations.**Practical Implication:** This study will be helpful in determining the disease severity prediction in patients suffering from COVID-19. For community benefit, this study will be important as it helps the people to determine either they are suffering from COVID-19 or not. It will also help them to take the necessary precautionary measures.**Conclusion:** The study concluded that there are several clinical predictors of COVID-19 like fever, old age anorexia, loss of taste, shortness of breath, and muscle aches. In addition, some laboratory markers such as serum ferritin, CRP level, total leucocyte count, and LDH are responsible for indicating the disease severity. Earlier disease prediction results in timely and early intervention, thereby helps in the prevention of progression toward critical stage.**Keywords:** Coronavirus disease 2019 (COVID-19), disease severity, mild and moderate disease, severe and critical disease**INTRODUCTION**

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2¹. It was first diagnosed in Wuhan, China, and declared a pandemic by WHO in March 2020 after its rapid spread across the globe, affecting millions of people with unexplained pneumonia². On Jan 30, 2020, 1st case of human-to-human transmission was reported in the USA. 1st calculated mortality rate was 2.2%^[3]. As of May 22, 2021, worldwide, 166,558,860 people were infected with SARS-CoV-2, with 3,459,929 deaths. In the USA, over 33 million people were infected with Covid-19, with over 0.6 million deaths. In the U.K., more than 4.4 million infected cases were reported, with 127,710 deaths. In Pakistan, 1,160,494 people were infected with COVID 19, with 20,177 reported deaths⁴.

Clinical studies on the severity of COVID-19 reported more than 50% mortality rate as the severity of the disease occurs in around 20% of infected cases^{5,6}. Furthermore, the severity of the disease leads to ARDS in approximately nine days⁷. Early identification of severe COVID-19 disease may lead to earlier interventions and thus decreases mortality. The National Health Commission of China has divided COVID-19 infected patients into mild, moderate, severe, and critical. Over 80% of these patients do not need any hospitalization, while a small number of these patients need specialized and supervised care. Patients with comorbidities are at risk of developing ARDS with multi-organ failure⁸. However, patients with mild or moderate diseases may even develop the severity of the illness with fatal outcomes. The National Health Commission of China has developed a complex system for analyzing severity in COVID-19, including blood gas analysis and imaging studies. Some of the routine measures, including duration of the disease, age of the patient, comorbidities, and some investigations like serum ferritin level, C-reactive protein, lactate dehydrogenase, and d-dimers, may predict the severity of the disease. Thus early identification of the severity may lead to proper, timely interventions.

This study aims to predict the severity indices in COVID-19 infected patients based on age, comorbidities, and laboratory investigations which may help update the local guidelines regarding the management plan of COVID-19 as currently limited local data is available on the topic.

MATERIAL AND METHODS

This case-control study was conducted in Khyber Teaching Hospital Peshawar, Pakistan, which is tertiary care hospital in Khyber Pakhtunkhwa from 1st April 2021 to 1st June 2021. This study was approved by the hospital's ethical and research committee. Written informed consent was taken from each patient. All the patients who fulfilled the inclusion criteria were assessed. PCR positive COVID-19 hospitalized patients were evaluated. Patients were divided into four categories based on the severity of COVID 19. The mild disease was defined as patients having clinical symptoms without any findings of pneumonia on imaging. Patients having fever along with respiratory symptoms were defined as having the moderate disease. Severe COVID 19 was defined as: patients having respiratory distress, respiratory rate (R.R.) >30 per minute, and oxygen saturation <93. Critical COVID-19 was defined as: those who needed care in ICU, shock, mechanical ventilation due to respiratory failure, and multi-organ failure. Mild and moderate disease group was taken as control while severe and critical disease group was taken as cases. Data was collected on pre-design proforma. During the collection of data, standard precautionary were followed. Relevant clinical examination was done after taking a complete history. Data were recollected at the clinical outcome, i.e., discharge/improvement, unimprovement or death of the patient. Data were entered into Excel and analyzed by SPSS version 22. Frequency and percentage were calculated for categorical variables, while for numerical variables, mean and standard deviation were calculated. For comparison of numerical variables, student t-test was used

while for the comparison of categorical variables. The Chi-square test was applied, keeping a p-value less than 0.05 being considered statistically significant.

RESULTS

Results of the study stated that there are several predictors associated with the severity of the COVID-19 condition which were assessed either through physical examination or through laboratory studies. These indicators detect the severity of the disease. According to different signs and symptoms patients are categorized into mild, moderate and severe conditions. They also demonstrate to have varying oxygen saturation, anorexia, shortness of breath and body pain (as shown in table no 1).

Laboratory studies also demonstrates to show variations in the ranges of different laboratory tests with TLC, LDH, Ferritin level, D dimers, and CRP level showing higher values in severe cases as compared to mild to moderate cases (as shown in table no 2). All the patients were gone through all the laboratory tests in order to discriminate about their level of severity associated with COVID-19. Out of these 140 patients, male and female patients were 76 (54.3%) and 64 (55.7%), respectively. The mean age was 57.81 years \pm 14.96 SD.

Table 1: Basic parameters of COVID-19 patients on arrival (n=140)

Parameters	Mild to moderate disease (n=71)	Severe to critical disease (n=69)	p-value
Gender	Male: 36(50.7%) Female: 35 (49.3%)	Male: 35 (50.7%) Female: 34 (49.3%)	P =0.404
Age (in years)	48.39 \pm 13.71 SD	67.51 \pm 8.73 SD	P < 0.0001
O2 saturation	94.63 \pm 2.94 SD	15.45 \pm 11.54 SD	P <0.0001
Comorbidities	No comorbidity 42 (59%) A single of comorbidity 23 (32.4%) Two comorbidities 2 (2.8%) >3 co morbidities 4 (5.8%)	No comorbidity 06 (8.8%) A single of comorbidity 02 (03%) Two comorbidities 13 (18.8%) >3 co morbidities 48 (69.5%)	P <0.0001
Fever	High grade 18 (25.4%) Low grade 35 (49.2%) No fever 18 (25.4%)	High grade 35 (50.7%) Low grade 28 (46.4%) No fever 06 (2.9%)	P < 0.02
Shortness of breath	Yes 09 (12.7%) No 62 (87.3%)	Yes 43 (62.3%) No 26 (37.7%)	P < 0.0001
Body aches	Yes 11 (15.5%) No 60 (84.5%)	Yes 46 (66.7%) No 23 (33.3%)	P < 0.0001
Anorexia	Yes 10 (14%) No 61 (86%)	Yes 28 (40.6%) No 41 (59.4%)	P < 0.0001
Loss of taste	Yes 09 (12.7%) No 62 (87.3%)	Yes 21 (30.4%) No 48 (69.6%)	P < 0.01

Table 2: Laboratory parameters for COVID 19 (n=140)

Parameters	Mild to moderate disease (n=71)	Severe/critical disease (n=69)	p-value
TLC count (cells/L)	13.12x 10 ³ \pm 59.26 x 10 ² SD	15.6x 10 ³ \pm 73.04 x 10 ² SD	P= 0.04
Ferritin level ng/mL	682.82 \pm 590.23 SD	1559.2 \pm 816.87 SD	P= 0.001
LDH (U/L)	547.50 \pm 344.09 SD	816 \pm 752.87 SD	P= 0.02
D Dimers	639.4 \pm 631.68 SD	1185 \pm 1139.78 SD	P= 0.04
CRP level (mg/dl)	31.87 \pm 81.77 SD	103.9 \pm 115.20 SD	P= 0.0001

Most of the patients, 67 (47.9%), were aged >61 years, followed by 57 patients (40.7%) in the age group of 41 to 60 years. Two patients (1.4%) were having age less than 12 years. Seventy-four patients (52.9%) were noted to have oxygen saturation less than 93. Eight patients (5.7%) were on ventilatory support, while 27 patients (19.3%) were on BiPAP. Nineteen patients (13.6%) were without oxygen support, while 47 patients (30.7%) were on NRM for oxygen support. Out of these patients, 116 patients (82.8%) presented with fever, 92 patients (65.7%) with comorbidities, 52 patients (37.14%) with shortness of breath, 57 patients (40.7%) with body and muscle aches, 38 patients (27.2%) with anorexia and 30 patients (21.4%) with loss of taste. On the basis of severity

of COVID-19, there were statistically significant differences between the two groups i.e., mild/moderate COVID-19, severe/critical COVID-19 on the basis of age (p <0.0001), oxygen saturation (p <0.0001), co-morbidities (p <0.0001), fever (p <0.02), shortness of breath (p <0.0001), body aches (p <0.0001), anorexia (p <0.0001), loss of taste (p <0.01), total white blood cell count (p <0.04), serum ferritin level (p <0.001), LDH (p <0.02), d-dimers (p <0.04) and CRP (P <0.0001) (table #1, #2)

DISCUSSION

This study aimed to find the markers for the disease severity in COVID-19. Most of the (54.3%) participants were male. The mean age was 57.81 years \pm 14.96 SD. Multiple comorbidities (p <0.0001), fever (p <0.02), shortness of breath (p <0.0001), body aches (p <0.0001), anorexia (p <0.0001) and loss of taste (p <0.01) were the independent clinical predictors for the severity of COVID-19 in this study. In laboratory parameters, TLC count (p <0.04), serum ferritin (p <0.001), LDH (p <0.02), d-dimers (p <0.04), and CRP (P <0.0001) were also independent predictors for the disease severity in our study.

Bhargava A et al. concluded in their study that comorbidities (p <0.05) and CRP (p <0.05) were independent predictors of disease severity in COVID-19-infected patients, which is consistent with the result of our study. A similar conclusion of CRP was stated by Tan L et al. as well^{9,10}.

Our study concluded that older age (p <0.0001) and multiple comorbidities were independent risk factors for the disease severity in COVID-19. The same statement was concluded by Yang AP et al., Alizandehsani R et al., and Gallo Marin B et al. that increasing age and multiple comorbidities are associated with the severity of COVID-19^{11,12,13}.

Shang W et al. concluded in their study that CRP, increasing age, and d-dimer were statistically significant for disease severity on arrival and were important predictors for the disease severity in COVID-19, which is consistent with the results of our study¹⁴. Zhou Y et al. also listed age (p <0.001), CRP (p <0.002), and d dimers (p <0.01) as independent predictors for severe pneumonia¹⁵.

Wu C et al. Listed serum ferritin as an independent risk factor (p <0.0001) for ARDS. Henry BM et al. conducted a meta-analysis and predicted that serum ferritin might serve as a clinical predictor for fatal and severe COVID-19^{16,17}. Gracia P et al. concluded that hyperferritinemia was associated with septicemia¹⁸. Thus, based on these studies, we listed it as an essential predictor for the severity of COVID-19, leading to bilateral pulmonary infiltrate and ARDS.

Henry BM et al. conducted a pooled analysis to compare LDH levels in 1206 patients among the severe or critical group with the less-severe group and concluded that 84.6% of patients in the severe group were raised LDH levels than 43.3% patients in the non-severe group¹⁹. Serum LDH level was also elevated in MERS (Middle East Respiratory Syndrome) and now in SARS, which reflects its role in detecting multi-organ failure and influences the outcome of the disease in cases of ARDS²⁰. Other different studies have concluded that LDH was a predictor of the worst result in hospitalized patients^{21,22}.

Severe infections like COVID-19 release LDH release as a result of cytokine-mediated tissue injury. As isozyme-3 of LDH is present in lung tissue, that is expected to release a greater amount of LDH due to ARDS and thus indicates the severity of the disease, which coincides with the conclusive statement of our study²³.

C-reactive protein, hepatic proteins, is a marker for acute inflammation. It is regulated transcriptionally by IL-1 and IL-6²⁴. It may represent the disease damage in ARDS as sequelae of abnormal status in acute inflammation²⁵. In a small cohort of twenty-seven patients, C-reactive proteins were significantly associated with C.T. scan findings of severe pneumonia in COVID-19. Poggiali E et al. concluded that CRP was related to respiratory failure (disease severity) in COVID-19, which is consistent with the results of our study. Similarly, raised CRP was positively correlated

with increased TLC count in Poggiali E et al., which is again compatible with our study²⁶. In our study, both CRP and raised TLC count were independent predictors for severe COVID-19.

In our study, body aches, fever, shortness of breath, anorexia, and loss of taste were the clinical predictors ($p < 0.05$) at the bedside for the disease severity in COVID-19. Similar results of the association of body aches, shortness of breath, anorexia, and loss of taste with the disease severity were reported in different research studies²⁷⁻²⁹.

CONCLUSION

This study concludes that clinical predictors like older age, fever, shortness of breath, anorexia, muscle aches, and loss of taste may predict the severity of COVID-19. At the same time, laboratory markers like total leucocyte count, serum ferritin, LDH, and CRP level indicate the severity of the disease. Earlier prediction of the disease severity leads to earlier and timely intervention, preventing the progression toward the critical stage at the initial steps. Thus, many precious lives can be saved.

Recommendation: Further studies both locally and internationally are recommended for further validation of these predictors.

Limitations of the study: Mild and moderate disease group was taken as control and decreased sample size was the study's main limitation.

Conflict of Interest: Nil

Financial Aid: Nil

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