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IDENTIFICATION OF PREDISPOSING RISK FACTORS OF COVID-19 SEVERITY; A DESCRIPTIVE STUDY

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Abstract:
Coronavirus disease 19 (COVID-19) severity data is highly variable and many factors were linked to increased severity. Owing to the dense population, varied demographic characteristics, and high burden of various diseases, it is important to identify risk factors resulting in severe COVID-19 in Pakistan. It was a descriptive study, and 652 COVID-19-positive patients were enrolled from Mayo Hospital Lahore and grouped into mild and severe cases. Demographic, clinical history and laboratory findings at the time of admission were collected. Data were analyzed using SPSS V21. The results indicated that the patients with age above 30 years showed a significant association with disease severity and with increasing every 10 years, the odds of disease severity became double. Further, male gender (OR 1.729, p 0.002), low socioeconomic status (OR 4.01, p <0.0001), diabetes mellitus (OR 2.52, p 0.001), hypertension (OR 1.81, p 0.01) and heart attack (OR 2.05, p 0.02) were significantly increasing disease severity. Interestingly, malarial history and smoking showed a significant association with a milder form of the disease. We conclude that young people (30 and above) were at significant risk of severe COVID-19 infection. Similarly, diabetes mellitus, hypertension and cardiovascular diseases were identified as independent risk factors for COVID-19 severity in Pakistan.

Keywords: COVID-19 severity, NCDs, Pakistan, Hypertension, Risk factors

1. Introduction

Coronavirus disease 19 (COVID-19) fatality data showed significant variation among different countries. Various risk factors like age, gender, and comorbidities have been associated with severe COVID-19 infection (1). Several studies showed that non-communicable diseases (NCDs) like hypertension, cardiovascular and coronary heart diseases, and diabetes mellitus complicated the management of COVID-19 resulting in increased morbidity and mortality (2–7). Similarly, reports showed the association of communicable diseases like hepatitis, malaria, and tuberculosis (TB) with COVID-19. A previous history of hepatitis and TB accentuated severe infection (7,8) while a history of malaria was associated with a reduced risk of COVID-19 (9).

Pakistan is a densely populated country (204.65 million individuals) and is facing a dual burden of various NCDs and infectious diseases (10–12). Diseases like diabetes mellitus and hypertension, are very common affecting about 26% and 37% respectively (10,13,14). Almost 0.3 to 0.4 million people die from cardiovascular diseases (CVDs) every year and this number is increasing (15). Similarly infectious diseases including hepatitis (B and C), malaria and TB are also prevalent (16–18). Moreover, behavioral risk factors like physical inactivity, tobacco consumption, and unhealthy diets along with economic disparities are also on the rise (19,20). Besides, a mixed sort of public attitude towards COVID-19 was observed and the majority of the population didn't consider it a serious issue (21). It was expected that Pakistan might have a higher risk of COVID-19 susceptibility and vulnerability.

Keeping in view above, the present study was conducted to explore the predisposing risk factor of COVID-19 infection and their association with the disease severity.

2. Material/Subjects/Patients and methods

2.1. Ethical Approval

The ethical approval was taken from the National Bioethics Committee (NBC) of Pakistan (NBC 528-COVID-39/20). Prior informed consent was taken from all participants, or their attendants and all formalities were followed as per the Declaration of Helsinki.

2.2. Study design and setting

It was a descriptive study in which patients were enrolled from Mayo Hospital Lahore. In-formation including symptoms and laboratory findings was retrieved from hospital records while epidemiologic and demographic data were obtained by structured interviews with patients or their attendants.

2.3. Sample size

A sample size of 652 individuals was calculated using an online tool i.e., OpenEPi taking 1 ratio of sample size and 2.3 risk/prevalence ratio with a 95% confidence interval.

2.4. Study Population

Study participants were COVID-19 PCR positive and were categorized as mild and severe using the following criteria.

Severe: COIVD-19 patients of either gender, aged 18 years old or older with any of the following features were considered as severe cases.

i. oxygen saturation at rest i.e., ≤93%
ii. Respiratory distress ≥30 breaths per min
iii. Ratio of partial pressure of arterial oxygen to a fractional concentration of oxy-gen-inspired air ≤300 mm Hg
iv. Any complications like respiratory failure, septic shock etc.

Mild: The Mild group was COVID-19 patients of either gender; aged 18 years old or older with mild or moderate symptoms including cough, fever etc.

2.5. Data collection

Participants were introduced to the study, its purpose, and details about the objectives, procedures, and possible consequences. Informed consent was taken from patients or their attendants.
A structured Performa was developed to collect data using STEPS tools as a template and was validated and pretested before data collection and had the following components:

Socio-demographic factors: Information on all socio-demographic factors like gender, age, occupation, education, household income and location of residence etc. were collected. The information regarding household possessions and average household income was collected to calculate the wealth index. The participants were categorized into low, middle and upper classes as described by Rafique *et al., 2014*(22).

2.6. Behavioral factors and disease history

Information about smoking status, physical activities, and underlying conditions including diabetes mellitus, hypertension, CVDs and COPD was taken. Besides, the previous history of hepatitis, malaria and TB was also record-ed. The BCG vaccination was confirmed by observing the scar on the upper arm.

2.7. Clinical and Laboratory findings

Data about the clinical symptom, presentation and laboratory findings of the enrolled participants were taken from the patient file.

2.8. Data analysis

All collected data were checked, entered, and cleaned. Analysis was done using SPSS version 20. Categorical and continuous variables were analyzed by chi-square ($\chi 2$) and student t-test respectively. The stepwise analysis model was implied. In step 1, the difference in clinical symptoms, comorbidities and laboratory findings among mild and severe cases was computed by using $\chi 2$. In step 2, an association of demographic characters with COVID-19 severity was computed by regression analysis which was used as covariates in subsequent analysis. The association of comorbidities and laboratory findings with disease severity was determined using the multinomial regression model. A p-value less than 0.05 was considered significant.

3. Results

3.1. Demographic, clinical and laboratory characteristics of the participants

Overall, 652 COVID-19 patients were enrolled including 326 mild and 326 severe cases. The mean age of the severe and mild cases was 56 (±15) and 42 (±14) years respectively. Severe cases were significantly older and most of them were male (69%). Significant difference among severe and mild cases was observed in terms of literacy level, socioeconomic status and BCG vaccination status (Table 1). Most of the clinical presentations including fever, cough, vomiting, diarrhoea etc. were common among both groups. Analysis of laboratory findings at the time of admission of severe and mild cases showed a significant difference in leucocyte (WBCs) and red blood cell (RBC) count and ALT.

Table 1. Demographic characteristics of the studied participants in Pakistan.

General Characteristics		All Participants	Mild	Severe	p-value
Age (Years)	Mean	48.78	41.98	55.58	<0.01
	SD	14.82	15.41	14.23	
Gender (n=652)	Male	415 (64%)	189 (58%)	226 (69%)	0.002
	Female	237 (36%)	137 (42%)	100 (31%)	

Marital Status (n=607)	Married	514 (85%)	212 (72%)	302 (96%)	< 0.00001
	Unmarried	93 (15%)	82 (28%)	11(4%)	
Qualification (n=645)	Illiterate	177 (27%)	81 (25%)	96 (30%)	0.0006
	Elementary	113 (18%)	44 (14%)	69 (21%)	
	Secondary	127 (20%)	61 (19%)	66 (21%)	
	College or more	228 (35%)	138 (42%)	90 (28%)	
Socioeconomic status(n=495)	Lower Class	289 (58%)	122 (46%)	167 (74%)	< 0.00001
	Middle Class	167 (34%)	123 (46%)	44 (19%)	
	Upper Class	39 (8%)	24 (8%)	15 (7%)	
BCG (n=615)	Yes	480 (78%)	228 (73%)	252 (83%)	0.002
	No	135 (22%)	84 (27%)	51 (17%)	
Tobacco consumption (n=652)	Yes	176 (27%)	106 (33%)	70 (21%)	0.001
	No	476 (73%)	220 (67%)	256 (79%)	
Exercise (n=595)	Yes	295 (49.5%)	149 (53%)	146 (47%)	0.15
	No	300 (50.5%)	134 (47%)	166 (53%)	

3.2. Distribution of Co-morbidities among COVID-19 participants

The study of the distribution of co-morbidities showed a significant difference in presence of diabetes mellitus, hypertension, hyperlipidemia, and history of heart attack among mild and severe cases. No significant difference is found for asthma, COPD, and cancer. Among various common infections like hepatitis, malaria, and TB, the previous history of malaria showed significant differences between mild and severe cases. The presence of one or more than one commodity was also more common among severe cases as compared to milder ones. (Table 2).

Table 2. Distribution of comorbidities and risk factors among COVID-19 patients of Pakistan (Mild vs Severe).

Co-morbidities	**Mild (326)**	**Severe (326)**	**χ2 p-value**
Diabetes	57 (17%)	127 (39%)	**<0.0001**
Hypertension	86 (26%)	136 (42%)	**0.00003**
Heart Attack	35 (11%)	66 (20%	**0.0007**
Hyperlipidemia	45 (14%)	59 (18%)	0.134
Asthma	14 (4%)	23 (7%)	0.127
Chronic Obstructive Pulmonary Disease (COPD)	8 (2%)	10 (3%)	0.632
Cancer	3 (1%)	2 (0.6%)	0.457
Hepatitis	22 (7%)	24 (7%)	0.759
Malaria	94 (29%)	68 (21%)	0.030
Tuberculosis	6 (2%)	12 (4%)	0.151
Number of Co-morbidities in one person			
Not any	211 (66%)	128 (39%)	**<0.0001**
Single	65 (20%)	104 (32%)	
Multiple	50 (50%)	94 (29%)	

3.3. Association of demographic characteristics and COVID-19 severity

The association of demographic factors with the severity of COVID-19 was computed by logistic regression in terms of Odds ratios. Analysis showed a significant difference within various age groups where the highest OR of 21.70 (p.00001) was seen for the age group of 60 and above followed by 14.04 (p <0.0001), 7.80 (p <0.0001) and 3.45 (p 0.001) for age groups i.e., 30-39, 40-49 and 50-59 years (Table 3). In terms of gender, males were found to be associated with the severe form of COVID-19 with an OR of 1.72 and a p-value of 0.002 (Table 3). Among marital status, OR of 10.16 was observed for the married group of people. Further, illiterate people showed an association with disease severity with an OR of 1.98 and p-value of 0.001 while people with elementary and secondary school education showed OR of 2.71(p <0.0001) and 1.80 (p 0.09) respectively. (Table 3). In the case

of socioeconomic status, low-er-class people were associated with COVID-19 severity with an OR of 4.01 and a p-value of <0.0001. No exercise habit was associated with an OR of 1.26 and a p-value of 0.15 (Table 3).

Table 3. Association of demographic factors and with the severity of COVID-19.

Risk Factors		**Odds ratio (95% CI) p-value**
Age	18-29 Years	Reference Category
	30-39Years	**3.47(1.61- 7.46) 0.001**
	40-49 Years	**7.80(3.81- 15.97) <0.0001**
	50-59 Years	**14.04(5.6.89-28.62) <0.0001**
	60 and above Years	**21.70(10.70-44.01) <0.0001**
Gender (Ref: Female	Female	Reference Category
	Male	**1.729(1.252-2.388) 0.002**
Tobacco Consumption	No	Reference Category
	Yes	**0.479(0.326-0.704) <0.0001**
Marital Status	Unmarried	Reference Category
	Married	**10.16(5.30-19.46) <0.0001**
Qualification	College or more	Reference Category
	Secondary	**1.80(1.16-2.79) 0.09**
	Elementary	**2.71(1.69-4.32) <0.0001**
	Illiterate	**1.98(1.33-2.95) 0.001**
Socioeconomic status	Middle Class	Reference Category
	Lower Class	**4.01(2.65-6.08) <0.0001**
	Upper Class	1.96(0.939-4.12) 0.07
Exercise	Yes	Reference Category
	No	1.26(0.91-1.74) 0.15

3.4. Association of Comorbidities and laboratory findings with COVID-19 severity

To compute the association of comorbidities and laboratory findings with the severity of COVID-19, multinomial logistic regression was performed. Results in block 1 are showing an association of comorbidities with the severity of COVID-19. ORs and p-values are adjusted with demographic features as covariates. Results indicated that diabetes mellitus was associated with the severe form of the disease with an ORadj of 2.52 and p-value of 0.01 while hyperlipidemia showed an ORadj of 1.13 with a p-value of 0.66. Hypertension and heart at-tack were found to be associated with ORadj of 1.81 and 2.05 respectively (p 0.01, 0.02). Asthma showed ORadj of 1.33 with a p-value of 0.56. COPD and cancer were found to be associated with ORadj of 1.40, 0.45 and p-values of 0.61, and 0.46 respectively (Table 4). The ORadj for hepatitis, TB and malaria history were 0.79, 2.03 and 0.56 respectively (Table 4). The presence of single comorbidity was found to be associated with the severe form of the disease with odds of 2.35 and a p-value of 0.002 while the presence of multiple comorbidities is associated with an OR of 2.39 and p-value of 0.002 (Table 4).

In block 2, results of association of laboratory findings with COVID-19 severity indicated that elevated WBCs count was associated with the severe form of the disease with ORadj of 2.76 and p-value of 0.009. Decreased RBCs and platelet count were found to be associated with ORadj of 0.24, 0.48 and p-value of 0.004, 0.17 respectively. Similarly, a low Hb level was associated with ORadj of 0.78 (p 0.50). Elevated bilirubin, ALT and AST showed ORadj of 0.23, 2.29 and 1.28 with p-values of 0.15, 0.34 and 0.72 respectively. Further in-creased levels of urea and creatinine were found to be associated with severe forms of the disease with odds of 1.67 and 1.47 respectively (p 0.55, 0.37). An elevated level of Na showed an ORadj of 0.78 with a p-value of 0.70 while an elevated K level showed an ORadj of 1.41 and a p-value of 0.51 (Table 4 and Figure 1).

Figure 1. Comparison of various laboratory parameters in COVID-19 patients (Mild vs Severe)

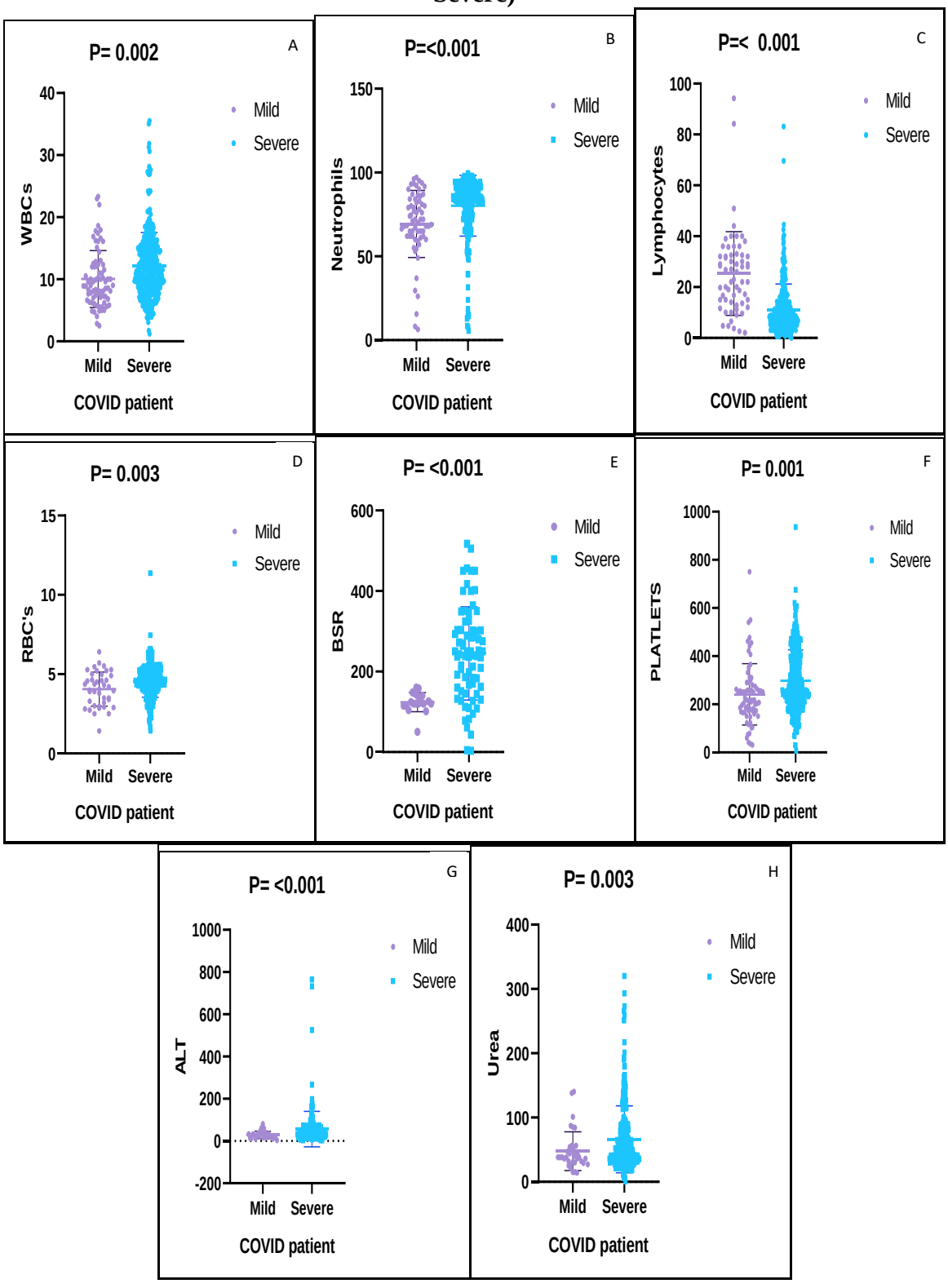

Figure 5. Comparative analysis of various parameters in COVID-19 patients (Mild vs Severe). (A) indicates the comparison of WBC's count in Mild and severe patients, B) indicates the comparison of Neutrophils count in Mild and severe patients, C) indicates the comparison of Lymphocyte count in Mild and severe patients, D) indicates the comparison of RBC's count in Mild and severe patients, E) indicates the comparison of BSR in Mild and severe patients, F) indicates the comparison of Platelet count in Mild and severe patients, G) indicates the comparison of ALT levels in Mild and severe patients, H) indicates the comparison of Urea concentration level in Mild and severe patients

Table 4. Demographic characteristics of the studied participants in Pakistan.

Block 1		
Co-morbidities	**Odds ratio (95% CI) p-value**	**Adjusted Odds ratio (95% CI) p-value***
Diabetes	**2.88 (1.99-4.15) <0.0001**	**2.52(1.49-4.24) 0.001**
Hypertension	**1.93 (1.37-2.71) <0.0001**	**1.81(1.11-2.93) 0.01**
Heart Attack	**2.5 (1.57-3.97) <0.0001**	**2.05(1.09-3.85) 0.02**
Hyperlipidemia	1.44 (0.93-2.21) 0.094	1.13(0.62-2.06)0.66
Asthma	1.29 (0.653-2.572) 0.45	1.33(0.49-3.58) 0.56
COPD	0.969 (0.377-2.49) 0.948	1.40(0.37-5.28) 0.61
Cancer	0.514 (0.085-3.102) 0.468	0.45(0.05-3.74) 0.46
Hepatitis	0.834 (0.456-1.526) 0.557	0.79(0.35-1.79) 0.58
History of Tuberculosis	1.573 (0.582-4.521) 0.375	2.03(0.52-7.86) 0.30
History of Malaria	0.839 (0.553-1.271) 0.406	**0.56(0.31-1.01) 0.055**
Number of comorbidities-Single	**2.65 (1.79-3.83) <0.0001**	**2.35(1.38-4.00) 0.002**
Number of comorbidities -Multiple	**3.08 (2.05-4.63) <0.0001**	**2.39(1.36-4.20) 0.002**
Block 2		
Laboratory Parameters	**Odds ratio (95% CI) p-value**	**Adjusted Odds ratio (95% CI) p-value***
Total WBC > 11000/uL	**2.61 (1.52-4.46) <0.0001**	**2.76(1.29-5.90) 0.009**
RBC < 4.2-6 million cells/uL	**0.37 (0.18-0.76) 0.007**	**0.24(0.09-0.63) 0.004**
Platelets count < 450,000/ul	0.505 (0.21-1.21) 0.12	0.48(0.16-1.38) 0.17
Hb < 12	1.28 (0.772-2.149) 0.332	0.78(0.37-1.6) 0.50
Bilirubin > 0.1-1.5	0.622 (0.129-3.000) 0.554	0.23(0.03-1.69) 0.15
ALT > 55	2.15 (0.585-7.95) 0.248	2.29(0.40-13.00) 0.34
AST > 33	1.346 (0.536-3.380) 0.527	1.28(0.32-5.11) 0.72
Urea > 24 mg/dL	1.28 (0.418-3.93) 0.665	1.67(0.30-9.30) 0.55
Creatinin > 1.2 mg/dL (N)	1.39 (0.732-2.667) 0.311	1.47(0.62-3.44) 0.37
Na >145 mEq/L	0.678 (0.254-1.809) 0.437	0.78(0.22-2.75) 0.70
K > 5 mmol/L	1.821 (0.808-4.107) 0.148	1.41(0.49-4.01) 0.51

*Adjusted with demographic factors

4. Discussion:

This study reports an association of demographic, clinical presentations, laboratory findings at the time of admission, comorbidities, and history of previous infections with COVID-19 severity.

A significant difference was found between the mean age of mild and severe cases where severe cases were older than milder ones. The disease severity was directly associated with age and the odds of the severity of the disease became greater with increased age. The highest probability of disease severity was seen in the age group of 60 and older but the young age groups i.e., 30 and above were also found to be at significant risk. By increasing every 10 years of age, the risk of severe COVID-19 infection becomes double. These findings are consistent with the previous studies in which age was reported as a major factor in increasing COVID-19 severity in different populations (23,24). It was shown that age alone is a major factor for COVID-19 severity without any comorbidity (25). These findings show that young people are at equal risk of developing a severe COVID-19 infection. Among gender, males showed significantly severe form as compared to females which is consistent with previous studies (26–28). The possible reasons for gender biasedness include high expression of angiotensin-converting enzyme-2, low expression of immunoglobulins in males and differential expression of sex hormones i.e. estrogen and testosterone (29,30). Moreover, lifestyle and sensible attitude toward disease in terms of hand washing, wearing masks and staying at home are different in both genders (26,31–33).

Association between smoking and COVID-19 severity has been reported previously (34–36). However, we could not establish any association of smoking with COVID-19 severity rather we found highly significant association of tobacco consumption with milder form of disease. This finding is supported by the previous research showing the reduced risk of dis-eases with smoking (37). Probably the anti-inflammatory effect of nicotine and reduce immune response may reduce the chances of a cytokine storm in COVID-19. Similarly, an in-creased level of nitric oxide might prevent the replication of SARS-CoV-2 in the respiratory tract and its entry into cells (34).

A significant difference has been found in terms of socioeconomic status as more severe cases belonged to the lower class. This might be because the lower class has less access to health care facilities including timely diagnostic testing and also various comorbidities (38–40) Moreover their overcrowded accommodation and less social distancing is also leading factor (41). Furthermore, qualification level also showed a significant association with illiterate and those having secondary education were more prone to severity. This might be due to the lack of information and the inability to report symptoms and health conditions (42).

Our analysis showed that diabetes mellitus, hypertension, and CVDs as independent risk factors of COVID-19 severity after adjusting with covariates. It has been reported that the COVID-19 severity is tripled among diabetics (43). Dysfunctional glucose homeostasis and immune system, possible overexpression of ACE2 and cytokinin, increased oxidative stress, abnormal vascular system and prothrombotic state might be the key factors resulting in severe COVID-19 among diabetic patients (44,45). The exact mechanism of hypertension in in-creasing risk is unclear. However, studies reported hypertension as an independent factor resulting in COVID 19 severity while some linked hypertension with COVID-19 only in old age (46–48). Similarly, the previous history of CVDs caused worse consequences in COVID 19 including evidence of myocardial injury (5). No association was found between hyperlipidemia, asthma, COPD, and cancers with COVID-19 severity. The Association of hyperlipidemia, asthma and COPD as risk factors for COVID-19 severity has varied in different studies (49–53).

Analysis of the history of hepatitis did not show any significant association with COVID-19 severity. This finding is inconsistent with the previous reports in which hepatitis has been identified as a risk factor to worsen the disease status of COVID-19 (54–59). In the case of malarial history, a milder form of infection has been observed in our study. Similar findings were also reported previously with a lower proportion of severe infection in African countries. The possible reason might be the strong innate immunity caused by endemics like plasmodium leading to robust immune responses against COVID 19 (9).

Previously, a link to TB has been reported in the case of COVID-19 (7, 60). We found that patients with a history of TB showed a trend of association with a severe form of disease however statistically remained insignificant.

Analysis of various laboratory findings at the time of admission showed a significant association between WBCs, and RBCs count. The elevated level of WBCs has been associated with severe disease and even death (61). This increase is probably related to the immune system dysregulation due to increased cytokine storm in severe infection (61, 62). Similarly, an increased level of bilirubin, ALT and AST in severe cases was seen which might be due to liver injury, associated inflammatory responses, muscle breakdown and congestive hepatopathy (63, 64). Increased level of urea and creatinine was also observed in severe cases. The previously elevated level was reported to be associated with death in COVID-19 (65). We also found low Hb levels and elevated Na and K levels in severe cases however these parameters remained statistically insignificant.

5. Conclusion:

We concluded that young age groups i.e., 30 years and above are at risk of acquiring severe COVID-19 infection like the elderly. Among NCDs, hypertension, diabetes mellitus, and CVDs were independent risk factors of COVID-19 severity. However malarial history and tobacco consumption were found to be associated with the milder form of the disease.

6. Acknowledgement

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7. Conflict of interest

The authors declare no conflict of interest

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