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Association of comorbidities with the COVID-19 severity and hospitalization: A study among the recovered individuals in Bangladesh

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ABSTRACT

Objectives: We aimed at the identification of the association of comorbidities with the COVID-19 severity and hospitalization.

Methods: It is a retrospective cross-sectional study to investigate the variation in age, sex, dwelling, comorbidities, and medication with the COVID-19 severity and hospitalization by enrolling 1025 recovered individuals while comparing their time of recovery with or without comorbidities.

Results: COVID-19 patients mostly suffered from fever. The predominant underlying medical conditions in them were hypertension (HTN) followed by diabetes mellitus (DM). Patients with cardiovascular disease (CVD) (54.3%) and hepatic disorders (HD) (43.6%) experienced higher severity. The risk of symptomatic cases was higher in aged (odds ratio, OR = 1.04, 95% CI = 1.02–1.06) and comorbid (OR = 1.87, 95% CI = 1.34–2.60) patients. T-test confirmed the differences between the comorbid and non-comorbid patients' recovery duration. The presence of multiple comorbidities increased the time of recovery (15–27 days) and hospitalization (20–40%). Increased symptomatic cases were found for patients having DM+HTN whereas CVD+Asthma patients were found with higher percentage of severity. Besides, DM+CKD (chronic kidney disease) was associated with higher hospitalization rate. Higher odds of severity were found for DM+CVD (OR = 4.42, 95% CI = 1.81–10.78) patients. Hospitalization risk was also increased for them (OR = 5.14, 95% CI = 2.02–13.07). Moreover, if they had HTN along with DM+CVD, they were found with even higher odds (OR = 6.82, 95% CI = 2.37–19.58) for hospitalization.

Conclusion: Our study indicates that people who are aged, females, living in urban area and have comorbid conditions are at a higher risk for developing COVID-19 severity. Clinicians and health management authorities should prioritize these high-risk groups to reduce mortality attributed to the disease.

Keywords: COVID-19, comorbidities, severity, hospitalization

Introduction

The outbreak of coronavirus disease (COVID-19), a disease caused by the infection of a novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first detected in Wuhan, China, at the end of December 2021.[1] Assessing the alarming levels of spread and severity, the World Health Organization (WHO) declared COVID-19 as a pandemic on March 11, 2020.[2] Alongside, the WHO recommended a handful of simple precautionary measures.[3] As the toughest action, many countries imposed nationwide COVID-19 lockdown – softer or harder restriction on the movement of people outside the home, except for the emergency personnel –to slow down the spread of the virus.[4]

Fortunately, an unprecedented speed, there are some good vaccines already developed and the WHO approved their

emergency use to control the pandemic.[5] Despite the COVAX initiative, led by CEPI, Gavi, and WHO, alongside key delivery partner UNICEF for global equitable access to COVID-19 vaccines,[6] least developed and lower-middle-income countries such as Bangladesh are still struggling to get sufficient vaccine to vaccinate at-risk people unlike the developed world. Intermittently, country-wide lockdown measures are imposed when the hospitals are overwhelmed with COVID-19 patients. Bangladesh is among the countries affected badly with COVID-19. The country has already reported more than 1.5 million laboratory confirmed cases with over 27 thousand deaths (as reported till November 24, 2021), and so far, the percentages of population fully vaccinated are only 20.6%.[7] Prioritization of COVID-19 patients who would require hospitalization in Bangladesh can be made by assessing he risk factors within the local socioeconomic status and demographic characteristics, although some risk factors on COVID-19 are already available in published literature, such as male gender,[8] aged people,[9] and people having other comorbidities.[10,11]

Despite multiple studies referred to above on association of comorbidity with severe COVID-19 illness, this subject still needs more investigations, particularly from resource-poor countries. This is also poorly understood from Bangladesh.[12–15] Realizing the low vaccination rate and ongoing COVID-19 pandemic progression and comorbidities driven aggressive consequences of patients, a good understanding on the association of risk factors with COVID-19 severity would be helpful for timely hospitalization of COVID-19 patients and to support those who need the most when resources are limited. Here, we describe the impact of comorbidities on COVID-19 severity and hospitalization by assessing the recovered patients in Bangladesh from the disease.

Methods

Study design, sites, participants, and data collection

The study included laboratory-confirmed COVID-19 patients who were diagnosed positive and later found to be negative at the Bangladesh Government Health Ministry designated COVID-19 test laboratory in Dhaka, Kushtia, Khulna, and Jessore by RT-PCR assay. The risk factors such as age, sex, dwelling, and comorbidities were considered to quantify the association between COVID-19 severity and hospitalization status. The recovery duration (days) was determined as the median days required for individuals tested negative from positive through RT-PCR assay. By following the guidelines from Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare (MOHFW), Bangladesh, and the World Health Organization, the symptoms of recovered patients were divided into four categories: Asymptomatic, mild, moderate to severe, and critical.[16] COVID-19 severities were compared between the recovered patients with or without preexisting comorbidity. We randomly included 1025 recovered individuals who provided completed data (November 2020–March 2021). The protocol was approved by the ethics committee, Chattogram Veterinary and Animal Sciences University (CVASU), Chattogram, Bangladesh (CVASU/DIR/(R & E)/EC/2020.191/1).

Statistical analysis

We used univariate, bivariate, and multivariate analyses. We used graphical presentation and tabular format to display the distribution of age, sex, and dwelling for identifying the pattern of the patients who suffered from COVID-19. We performed the bivariate analysis to compare age, hospitalization, and comorbidities between male and female. Chi-square test was performed to test the association between the categorical variables (sex, dwelling, and comorbidities) while Student's t-test was used to explore the significance of the mean difference of the continuous variables (age and recovery duration). In multivariate analysis, we performed three regression models to assess the influencing factors of three outcome variables such as symptomatic cases (Model 1), severity of the symptoms (Model 2), and hospitalization status (Model 3). The binary logistic regression model was used to estimate each model of interest. It is noted that the outcome variable "severity of the symptoms" was defined as "severe" if the patients reported the severity level of the symptoms as "moderate to severe" or "critical" and as "not severe" if the patients reported the severity level as "mild" or they were asymptomatic. The explanatory variables were age (in years), sex (male vs. female), habitation status (urban vs. village), having any comorbidity, having DM (diabetes mellitus), HTN (hypertension), CVD (cardiovascular disease), HC (hypercholesterolemia), RA (rheumatoid arthritis), HD (hepatic disorder), CKD (chronic kidney disease), and having allergic condition. We considered the odds ratios (ORs), 95% confidence interval (CI), and P values for the variables in the models. In the case of all statistical analyses, we assumed significance only if $P < 0.05$. We performed the statistical analysis using SPSS (version 25).

Results

An overview on the demography of the patients enrolled

According to demographic data, 31.4% of patients were aged 31−40 years old represented in the supplementary information (SI), Figure 1A. Eventually, more than 70% of total patients were in the 21−50 years age range. The present study also revealed that the degree of severity of COVID-19 increased with increasing age and the incidence of asymptomatic cases decreased with increasing age [SI Figure 1B]. The percentages of male and female patients were 58.8% and 30.4%. However,

severities of the symptoms were found to be almost equal regardless of sex [SI Figure 1B]. About 90.0% of patients were urban dwellers likewise around the world [SI Figure 1A].[17] Among villagers and urban dwellers, there were a significant difference in case severity ($P = 0.035$).

Prevalent symptoms

There were about 9.2% (n = 94) of patients who were asymptomatic whereas 1, 2, 3, 4, 5, and 6 symptoms were predominant in 7.3%, 14.4%, 18.5%, 15.6%, 13.3%, and 8.8% of the patients, respectively [SI Figure 2]. Those with 3+ symptoms were on average 38.5 years old. The most prevalent clinical symptom was fever (82.8%) [Figure 1] which is in line with the observations reported earlier.[14,18] The order of the symptoms were observed as fever (82.8%) > no taste (ageusia)/smell (anosmia) (55.1%) > cough (51.0%) > fatigue > (39.3%) > sore throat (31.2%) > pain in body (30.9%) > diarrhea (24.6%) > dyspnea (23.0%) > sneezing (17.2%) > vomiting (11.9%) > headache (6.0%) > conjunctivitis (5.8%) > reduction in oxygen level (ROL) (5.3%) > body pain with fever (BPF) (4.9%) > chest pain (1.0%). In addition, some other rare symptoms were also observed like memory loss (0.017%), hair fall (0.01%), and excessive sweating (0.006%). Fever was the most prevalent symptom for both males (83.4%), females (78.2%), and among all age groups [SI Table 1].

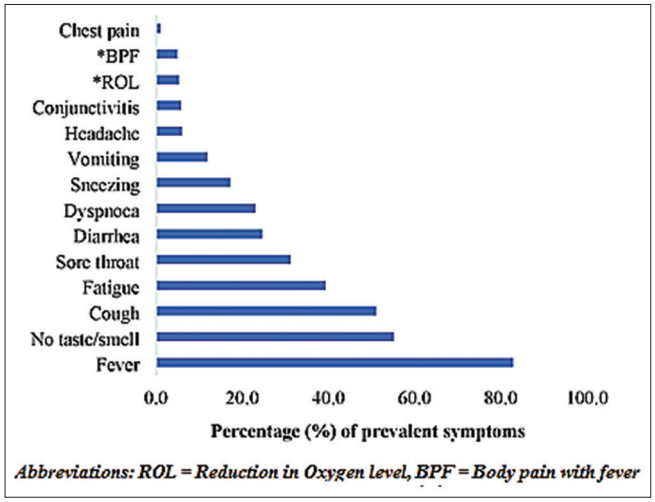

Figure 1: Prevalent symptoms in COVID-19 cases in Bangladesh, 2020–2021

Distribution of comorbidities

Specific comorbidities – HTN was the most common preexisting comorbidities among the patients [Table 1]. The least common comorbidity was CKD (2%). In terms of comorbidities and COVID-19 severity, patients with CKD, asthma, and HTN suffered from critical conditions, proportionately 6.3%, 7.1%, and 5.1%, respectively. Patients with DM, CVD, HTN, and HC were found with variable degree (30–35%) of moderate-to-severe cases. About 50.9% of the female patients had comorbidity which was higher than that of the male patients (43.4%) [SI Table 2].

Preexisting comorbidities and recovery period

The recovery period of the patients with four or more comorbidities was longer (18 ± 6.6 days) compared to those with no or less than 2 comorbidities [Figure 2a]. Patients with no comorbidity had faster recovery (15.5 ± 6.1 days) where patients having 1, 2, and 3 comorbidities required 16 ± 9.7, 16 ± 10.2, and 17 ± 5.7 days, respectively [Figure 2a]. Comorbidities were identified as independent risk factors when analyzing the recovery period. Moderate-to-severe patients required more

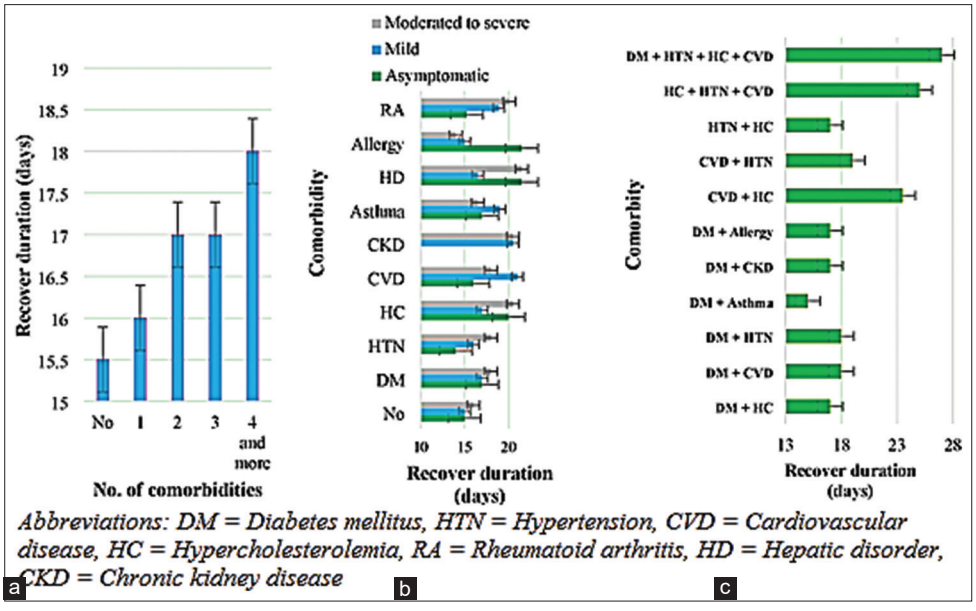

Figure 2: Impact of comorbidities on the recovery duration attributed to (a) number of comorbidities, (b) specific comorbidity, and (c) combination of comorbidities

Table 1: Distribution of comorbidities in COVID-19 patients, Bangladesh, 2020–2021

	Population	Asymptomatic (%)	Mild (%)	Moderate to severe (%)	Critical (%)	Remarks (%)
Total	1025	94 (9.2)	648 (63.2)	264 (25.8)	19 (1.9)	-
Comorbidities						-
No	558	64 (11.5)	386 (69.2)	101 (18.1))	7 (1.3)	
Yes	467	30 (6.4)	262 (56.1)	163 (34.9)	12 (2.6)	
No. of comorbidities						
1	238	20 (8.4)	147 (61.8)	67 (28.2)	4 (1.7)	HTN (22.0%), DM (19.3%), HC (10.7%), asthma (8.2%), RA (8.1%), HD (5.0%), CVD (4.5%), allergy (3.0%), and CKD (1.8%).
2	122	3 (2.5)	70 (57.4)	47 (38.5)	2 (1.6)	
3	69	5 (7.2)	28 (40.6)	33 (47.8)	3 (4.3)	
4	24	0 (0.0)	9 (37.5)	13 (54.2)	2 (8.3)	
>4+	14	2 (14.3)	8 (57.1)	3 (21.4)	1 (7.1)	
Total	467	30 (6.4)	262 (56.1)	163 (34.9)	12 (2.6)	
*Specific comorbidities						
HTN	171	5 (2.9)	107 (62.6)	54 (31.6)	5 (2.9)	*P*<0.001 (0.14–0.19)
DM	149	4 (2.7)	82 (55.0)	61 (40.9)	2 (1.3)	*P*<0.001 (0.12–0.17)
HC	83	5 (6.0)	39 (47.0)	37 (44.6)	2 (2.4)	*P*<0.001 (0.06–0.10)
Asthma	64	8 (12.5)	28 (43.8)	24 (37.5)	4 (6.3)	*P*<0.001 (0.05–0.08)
RA	63	6 (9.5)	33 (52.4)	23 (36.5)	1 (1.6)	P<0.001 (0.05–0.12)
HD	39	4 (10.3)	16 (41.0)	17 (43.6)	2 (5.1)	*P*<0.001 (0.03–0.05)
CVD	35	3 (8.6)	12 (34.3)	19 (54.3)	1 (2.9)	*P*<0.001 (0.02–0.05)
Allergy	23	2 (8.7)	15 (65.2)	6 (26.1)	0 (0.0)	*P*<0.001 (0.02–0.04)
CKD	14	0 (0.0)	8 (57.1)	5 (35.7)	1 (7.1)	*P*<0.001 (0.01–0.02)
Severity order for comorbidities						
Asthma, allergy, DM, HC		Mild>Moderate to severe>Asymptomatic>Critical				
HD, CVD		Moderate to severe>Mild>Asymptomatic>Critical				
CKD		Mild>Moderate to severe>Critical>Asymptomatic				
HTN		Mild>Moderate to severe>Asymptomatic>Critical				
No comorbidity		Mild>Moderate to severe>Asymptomatic>Critical				

DM: Diabetes mellitus, HTN: Hypertension, CVD: Cardiovascular disease, HC: Hypercholesterolemia, RA: Rheumatoid arthritis, HD: Hepatic disorder, CKD: Chronic kidney disease

time to recover than that of mild and asymptomatic patients who had comorbidities [Figure 2b]. Asymptomatic patients who had DM, HTN, CVD, asthma, and RA required <17 days to recover where other patients required higher duration (20 ± 6.0, 21.5 ± 3.9, and 21.5 ± 2.1 days for HC, HD, and allergy). Moderate-to-severe patients with HD (21.5 ± 5.7 days), HC (20.5 ± 8.2 days), HTN (18 ± 12.4 days), DM (18 ± 12.3 days), and CVD (18 ± 9.5 days) required at least 18 median days to recover. Moreover, patients with multiple comorbidities such as DM, HTN, HC, and CVD required 27 days compared with 15.5 days in patients without those comorbidities [Figure 2c].

Preexisting comorbidities and hospitalization

We found that the likelihood of hospitalization was 28.5% in patients with preexisting CVD, 27.6% in patients with DM, and 24% in patients with RA [Figure 3a]. The hospitalization proportion ranged from 15% to 18% in the patients with asthma, CKD, HTN, and HC [Figure 3a]. Significant association of hospitalization with DM ($P < 0.001$), CKD ($P < 0.001$), CVD ($P < 0.001$), and HTN ($P = 0.002$) was found [SI Table 3]. When patients suffered from DM combined with CVD and HTN, 40% of them required hospitalization [Figure 3b]. About 33% of patients who suffered from HTN and HC plus CVD with DM required hospitalization. The proportion of patients with CVD plus HTN required hospitalization was 40%, the highest percentage. Individually, the presence of DM and CVD was associated with a higher rate of hospitalization (35.2% and 28.5%, respectively).

Medication history

Of the patients' information analyzed, 94.0% ($P < 0.001$) took medicines, and majority of them took multiple drugs. For instance, around 92.7% of the patients took both antipyretics and antibiotics [SI Table 4]. The used drugs could be ordered as antipyretic (93.9%) > antibiotic (92.7%) > antihistamine (84.9%) > antiviral (83.0%) > steroid (82.3%).

Hospitalization history with age, sex, and dwelling

In the present study, the proportion of hospitalization was higher in patients of >40 years of age compared with the younger

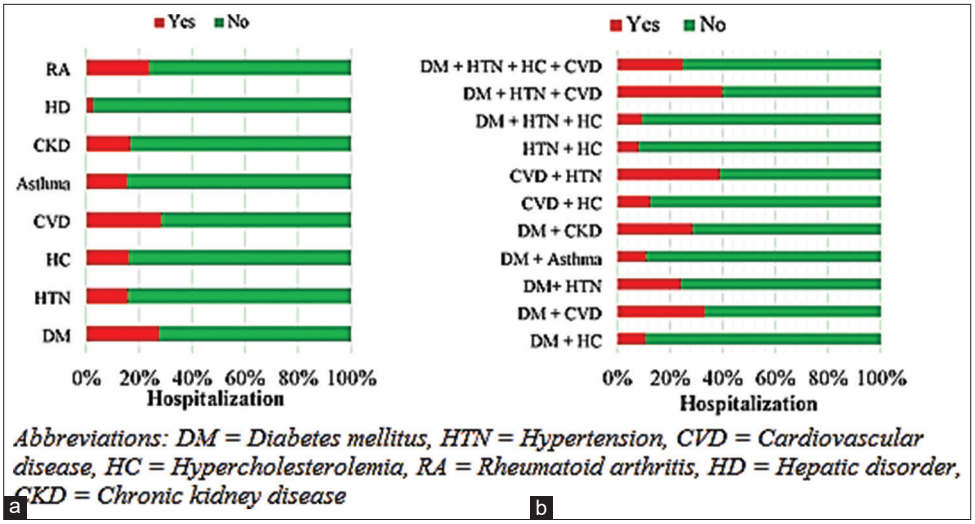

Figure 3: Hospitalization history of patients with different comorbidities; (a) individual comorbidities and (b) combination of comorbidities

counterparts (5%) [SI Figure 3]. We observed that the rate of infection in women was significantly lower compared with men [SI Figure 1A]. We observed 7.8% of the male and 13.5% of the female patients required hospitalization. On the other hand, the rate of hospitalization in male patients with comorbidity (64%) was higher compared with the female patients (54.8%) [SI Table 2]. The proportion of people admitted to hospitals in towns (10%) is higher than that in villages (6.7%).

Chi-square test, t-test, and optimum regression model

A Chi-square test for independence with $\alpha = 0.05$ was used to assess whether sex, habitation, and comorbidity were related to the degree of severity and hospitalization [SI Table 5]. While tested for degree of severity, the Chi-square tests were found statistically significant for sex, ($\chi^2 = 9.306$, $P < 0.05$, $\phi = 0.010$), habitation, ($\chi^2 = 5.223$, $P < 0.05$, $\phi = 0.202$), and comorbidity, ($\chi^2 = 41.756$, $P < 0.05$, $\phi = 0.202$). However, hospital admission was related to sex ($\chi^2 = 11.239$, $P < 0.05$, $\phi = 0.105$) and comorbidity ($\chi^2 = 10.793$, $P < 0.05$, $\phi = 0.103$). Thus, the null hypotheses were rejected and the relation of these indicators with severity and hospitalization was established.

An independent samples t-test was used to compare the mean recovery duration of comorbid and non-comorbid patients [SI Table 6(a) and 6(b)]. It was assumed that there is no significant difference among the comorbid and non-comorbid patients' recovery duration. We found this null hypothesis to be rejected. Neither Shapiro–Wilk statistic was significant, indicating that the assumption of normality was not violated. Levene's test was also insignificant; thus, an equal variance can be assumed for both groups. The t-test was statistically significant, with mean recovery duration of comorbid patients (M = 19.52, SD = 9.06) was significantly higher (mean difference –2.01778, 95% CI [−3.01165, −1.02390]) than the non-comorbid patients (M = 17.51, SD = 6.10), t = −3.984, $P < 0.001$, two tailed.

Binary logistic regression was performed to assess the impact of several factors on the likelihood that respondents would report for degree of severity and hospital admission [SI Table 7, 8(a) and 8(b)]. To perform binary logistic regression, we considered multiple predictor variables (sex, age, habitation, and comorbidities) and one response variable (degree of severity or hospital admission) using the following formula to estimate the relationship between the variables:

$$\log \frac{p(x)}{1-p(x)} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots\ldots + \beta_k x_k$$

Multiple logistic regression uses the following null and alternative hypotheses:

$$H_0 : \beta_1 = \beta_2 = \ldots\ldots\ldots = \beta_k = 0$$

$$H_1 : \beta_1 = \beta_2 = \ldots\ldots\ldots = \beta_k \neq 0$$

The null hypothesis states that all coefficients in the model are equal to zero. In other words, none of the predictor variables have a statistically significant relationship with the response variable, y. Forward regression model was found to be the best fit for obtaining the optimal model [SI Table 7]. The model contained four independent variables (sex, age, habitation, and comorbidity status). The full model containing all predictors was statistically significant for degree of severity ($\chi^2 = 53.673$, $P < 0.001$) with −2log likelihood ratio of 1154.248. However, 79% of the variance of the dependent variable being studied was explained by the variance of the independent variable [$R^2 = 0.79$]. Similar observation was found for hospital admission ($\chi^2 = 125.520$, $P < 0.001$) with −2log likelihood ratio of 511.869 and $R^2 = 0.82$.

Association of the risk factors

After the univariable analysis, the variable aged COVID-19 patient was found to be positively associated with

symptomatic cases (OR = 1.04, 95%CI = 1.02−1.06, *P* = 0.001), development of severity (OR = 1.02, 95%CI = 1.00−1.04, *P* = 0.025), and higher hospital admission rate (OR = 1.05, 95%CI = 1.02−1.07, *P* < 0.001) [Table 2]. Male patients were negatively associated with the development clinical symptoms (OR = 0.66, 95%CI = 0.49−0.90, *P* = 0.008), severity (OR = 0.64, 95%CI = 0.47−0.88, *P* = 0.006), and need for hospitalization (OR = 0.58, 95%CI = 0.34−0.97, *P* = 0.039) compared with female. Patients with comorbid conditions had a higher risk of developing symptoms (OR = 1.87, 95%CI = 1.34−2.61, *P* < 0.001) and severity (OR = 1.85, 95%CI = 1.32−2.60, *P* < 0.001). The results of multivariable logistic regression analysis revealed that the risk of developing clinical symptoms was higher in patients with DM (OR = 3.54, 95%CI = 1.24−10.15, *P* = 0.019), HTN (OR = 3.45, 95%CI = 1.35−8.83, *P* = 0.010), CVD (OR = 2.55, 95%CI = 1.17−5.58, *P* = 0.019), HD (OR = 2.36, 95%CI = 1.17−4.75, *P* = 0.016), and asthma (OR = 1.94, 95%CI = 1.09−3.45, *P* = 0.025).The variable urban population was positively associated with the development of clinical symptoms (OR = 1.20, 95%CI = 1.05−2.51, *P* =.038). The comorbidity variable CVD had the highest impact in developing clinical severity (OR = 2.67, 95%CI = 1.29−5.53, *P* = 0.008), followed by asthma (OR = 2.28, 95%CI = 1.34−3.86, *P* = 0.002), HD (OR = 2.14, 95%CI = 1.09−4.20, *P* = 0.028), and DM (OR = 1.68, 95%CI = 1.13−2.48, *P* = 0.011).

However, comorbidity variable CVD and DM mellitus had positive but almost a similar impact on the requirement for hospitalization (OR = 2.40, 95% CI = 1.03−5.62, *P* = 0.043 vs. OR = 2.54, 95% CI = 1.49−4.35, *P* = 0.001). On the contrary, the risk for the need for hospitalization was found lower in COVID-19 patients with HC (OR = 0.28, 95%CI = 0.8−0.99, *P* = 0.047). Furthermore, multiple comorbidities were found to be associated with severity and hospitalization. Patients with preexisting DM plus CVD had higher risk for severe symptoms (OR = 4.42, 95%CI = 1.81–10.78, *P* = 0.001) or hospitalization (OR = 5.14, 95%CI = 2.02–13.07, *P* = 0.001). Similarly, preexisting DM plus HTN increased risk for severity (OR = 2.25, 95%CI = 1.31–3.84, *P* = 0.003) and hospitalization (OR = 3.43, 95%CI = 1.81–6.53, *P* < 0.001). In addition, patients having DM and CVD plus HTN conjointly had 4.03-times odds for severe symptoms (OR = 4.03, 95%CI = 1.42–11.43, *P* = 0.009) where risk for hospitalization was also very high (OR = 6.82, 95%CI = 2.37–19.58, *P* < 0.001) than the patients without those comorbidities.

Discussion

COVID-19 is still causing health stress around the world. Health conditions and comorbid diseases have been studied in developed countries for their impact on severity of disease and the necessity for hospitalization.[19,20] However, a developing country like Bangladesh has not fully grasped this issue.[13-15] We, therefore, conducted a study to investigate

Table 2: Association of the risk factors with COVID-19 symptomatic cases, severity, and hospitalization*

Variables	Categories	OR (95% CI)	*P*
Model 1: Symptomatic case (1=Yes, 0=Otherwise)			
Age (in years)	-	1.04 (1.02−1.06)	0.001
Sex	Male	0.66 (0.49−0.90)	0.008
Habitation	Urban	1.61 (1.03−2.52)	0.038
Comorbidity	Yes	1.87 (1.34−2.61)	0.000
DM	Yes	3.54 (1.24−10.15)	0.019
HC	Yes	1.68 (0.96–2.95)	0.072
Asthma	Yes	1.94 (1.09–3.45)	0.025
HD	Yes	2.36 (1.17–4.75)	0.016
CKD	Yes	0.69 (0.19–2.48)	0.569
CVD	Yes	2.55 (1.17–5.58)	0.019
Allergy	Yes	0.89 (0.35–2.25)	0.800
HTN	Yes	3.45 (1.35–8.83)	0.010
DM+CVD	Yes	2.04 (0.27–15.37)	0.489
DM+HTN	Yes	2.94 (0.71–12.62)	0.138
DM+HTN+CVD	Yes	1.42 (0.19–10.92)	0.736
Model 2: Severity of the symptoms (1=Severe, 0=Not severe)			
Age (in years)	-	1.02 (1.00−1.04)	0.025
Sex	Male	0.64 (0.47−0.88)	0.006
Habitation	Urban	1.20 (1.05−2.51)	0.038
Comorbidities	Yes	1.85 (1.32−2.60)	<0.001
DM	Yes	1.68 (1.13–2.48)	0.011
HC	Yes	2.00 (1.22–3.28)	0.006
Asthma	Yes	2.28 (1.34–3.86)	0.002
HD	Yes	2.14 (1.09–4.20)	0.028
CVD	Yes	2.67 (1.29–5.53)	0.008
Allergy	Yes	0.89 (0.359–2.22)	0.808
HTN	Yes	0.75 (0.50–1.13)	0.169
DM+CVD	Yes	4.42 (1.81–10.78)	0.001
DM+HTN	Yes	2.25 (1.31–3.84)	0.003
DM+HTN+CVD	Yes	4.03 (1.42–11.43)	0.009
Model 3: Hospitalization status (1=Hospitalized, 0=Otherwise)			
Age (in years)	–	1.05 (1.02−1.07)	<0.001
Sex	Male	0.58 (0.34−0.97)	0.039
Habitation	Urban	1.15 (0.56–2.39)	0.705
DM	Yes	2.54 (1.49−4.35)	0.001
HC	Yes	0.28 (0.08−0.99)	0.047
Asthma	Yes	1.80 (0.73−4.48)	0.204
HD	Yes	0.51 (0.10−2.51)	0.407
CKD	Yes	2.99 (0.70−12.70)	0.138
CVD	Yes	2.40 (1.03−5.62)	0.043
Allergy	Yes	0.61 (0.08−4.84)	0.641
HTN	Yes	1.70 (0.84−3.42)	0.138
DM+CVD	Yes	5.14 (2.02–13.07)	0.001
DM+HTN	Yes	3.43 (1.81–6.53)	<0.001
DM + HTN + CVD	Yes	6.82 (2.37–19.58)	<0.001

DM: Diabetes mellitus, HTN: Hypertension, CVD: Cardiovascular disease, HC: Hypercholesterolemia, RA: Rheumatoid arthritis, HD: Hepatic disorder, CKD: Chronic kidney disease. *P*<0.05 is statistically significant at two-tailed test

the association between comorbid diseases and COVID-19 severity. In this cohort, the majority of patients were in the 21−50 years old range signified that larger number of working-age people exposed to outside with greater possibilities of infection due to COVID-19 which was seen across the globe including Bangladesh.[21-24] This finding further reflected that young patients are more prevalent in Bangladesh. This study also confirmed that serious COVID-19 complications are closely associated with the eldest patients due to their weak immune responses. Zimmermann *et al*. reported that serious COVID-19 complications are closely associated with the eldest patients due to their weak immune responses.[25] The previous studies have also reported an increased infection rate among males.[26,27] Globally, most of the patients were urban dweller which could be due to living in the dense area as well as using public transport, etc.[28] In our study, we detected that male and urban patients were dominant in similarity with the previous report.[16,27,28] The most prevalent clinical symptoms were fever and no taste (ageusia)/smell (anosmia) which is in line with the observations reported earlier.[14,18]

Numerous reports revealed that people with multiple preexisting comorbidities were at an increased risk for COVID-19 severity.[29-32] Notable that, H7N9, SARS-CoV, and MERS-CoV caused severe illness mostly in patients with preexisting comorbidities.[33] As presented in this report, it was observed that higher numbers of comorbidities could lead to the development of critical conditions. Patients with a single comorbidity were less likely to develop critical symptoms (1.7%) compared with patients having 4 comorbidities (8.3%). Moreover, the proportions of asymptomatic patients decreased as the number of comorbidities increased (8.4% and 0.0% asymptomatic cases for 1 and 4 comorbidities, respectively) whereas it was 11.5% without comorbidities [Table 1], in conformity with previous reports, suggesting that comorbidities substantially exacerbate COVID-19 complexity.[34,35] We found that preexisting DM, HTN, CVD, HD, and asthma were associated with an increased risk of symptomatic cases in COVID-19 patients, similar to reports from some other previous studies conducted elsewhere.[29,33] Moreover, on the severity scale, CVD, asthma, HD, HC, and DM ranked highest in line with the previous studies.[29,30] In addition, the results of our study confirmed the findings of the previous studies demonstrating severe clinical consequences when multiple comorbidities exist.[13-15] Of note, patients with comorbidity had median age 45 (min. 6–max. 80, SD ± 12.8) years, and the median age of the patients without comorbidity was 31 years (min. 2–max. 70, SD ± 10.7). This further signified a higher possibility of having comorbidity with the increased age which ultimately could lead to a higher severity of COVID-19. A substantial impact of preexisting comorbidities was found on the recovery period (median days to recover) according to t-test. Similar results were also observed globally.[34,35] Moderate-to-severe patients with HD, HC, HTN, DM, and CVD required higher duration to recover in contrast to other comorbidities. Moreover, patients having multiple comorbidities required even more times. This is consistent with previous reports that HTN, DM, CVD, liver, and CKD directly affected the disease severity and recovery.[31,36] Although the mechanism of the phenomenon was unclear, variation of the innate immune system and medication history associated with specific comorbidities could play a role.[37] In general, aged peoples were more likely to be affected with different comorbidities, which, in turn, could weaken their innate immune system.[38]

On the other hand, the proportion of hospitalization was higher in patients of >40 years of age. We observed that the rate of infection in women was significantly lower compared with men in agreement with other reports.[14,15] However, surprisingly, once infected, the rate of hospitalization in female patients was higher compared with male. This was perhaps never reported before from any South Asian countries. This needs to be verified further by employing a broader sample size and to find out the cause behind the reported aggravation of physical conditions in female patients in Bangladesh after becoming infected. Our findings indicating that the average age of the female patients hospitalized was 42.5 ± 12.9 years which was higher than the average age of the patients enrolled (36.1 ± 13.4 years). However, weaker immune status due to malnourishment, age, and sex plus comorbidity could be the plausible reasons.[39] The proportion of hospitalization in the patients living in the urban areas (10%) was higher compared with the patients from rural areas (6.7%) in similarity with the previous studies.[14,15] Possibility of higher innate immune response in village people against SARS-CoV-2 was a debating issue until the mass spread of the delta variant of the virus in South Asian countries, but the difference in the rate of hospitalization could also be related to available and better health care facilities in the urban areas.[39] Hospitalization trend of the patients who were underlying health conditions can be ordered as CKD > DM > CVD > asthma > HTN whereas having multiple comorbidities put most at risk for hospitalization. Particularly, patients with DM along with CVD and HTN were found to be hospitalized most. These findings of the association of demographic factors, symptoms and comorbidities with the symptomatic case, severity, and hospitalization of COVID-19 patients reflect previous published findings.[20,31,34,39] It is imperative to examine underlying medical conditions of patients with COVID-19 to identify the risk group quickly. One of the conclusions from this study emphasizes the importance of providing immediate medical treatment to aged patients regardless of sex in Bangladesh who possess COVID-19 and comorbidities.

Conclusion

The occurrence of clinical symptoms, development of severity, and hospital admissions are higher among the older, female, and urban COVID-19 patients. Fever is the prevalent symptoms in both males and females of all ages. The commonly encountered comorbidities among COVID-19 patients in Bangladesh are HTN, DM, HC, and asthma. However, patients with CVD, asthma, CKD, and DM could have a

higher probability toward the development of severity that would require hospitalization. The presence of multiple comorbidities is associated with longer recovery time, severity, and hospitalization. The study recommends rapid response for older, female, and comorbid patients regardless of sex. In future, studies including more population and different center with the clinical data should be performed to power up the statistical analysis and to explore the association between comorbidities with the clinical data coupled with severity and hospitalization due to COVID-19.

Authors' Declaration Statements

Ethics approval and consent to participate

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials. Participants gave their consent to participate willingly.

Consent for Publication

Participants gave their consent for publication of analyzed data provided that their identity will not be disclosed publicly.

Availability of Data Material

The data used in this study are available and will be provided by the corresponding author on a reasonable request.

Competing Interests

The authors declare no conflicts of interest.

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Authors' Contributions

(I) Conception and design: S. Ganguli, S. Howlader, S. Barua, K. Dey, M.N. Islam, and P.K. Biswas; (II) Administrative support: S. Ganguli, S. Barua, and K. Dey; (III) Provision of study materials or patients: K. Dey and P.B. Partho, and R.R. Chakraborty; (IV) Collection and assembly of data: S. Howlader, M.D.H. Hawlader, B. Barua, T.H. Aquib, and P.B. Partho; (V) Data analysis and interpretation: S. Ganguli, M.D.H. Hawlader, P.K. Biswas, R.R. Chakraborty, and B. Barua; (VI) Manuscript writing: All authors; and (VII) final approval of manuscript: All authors.

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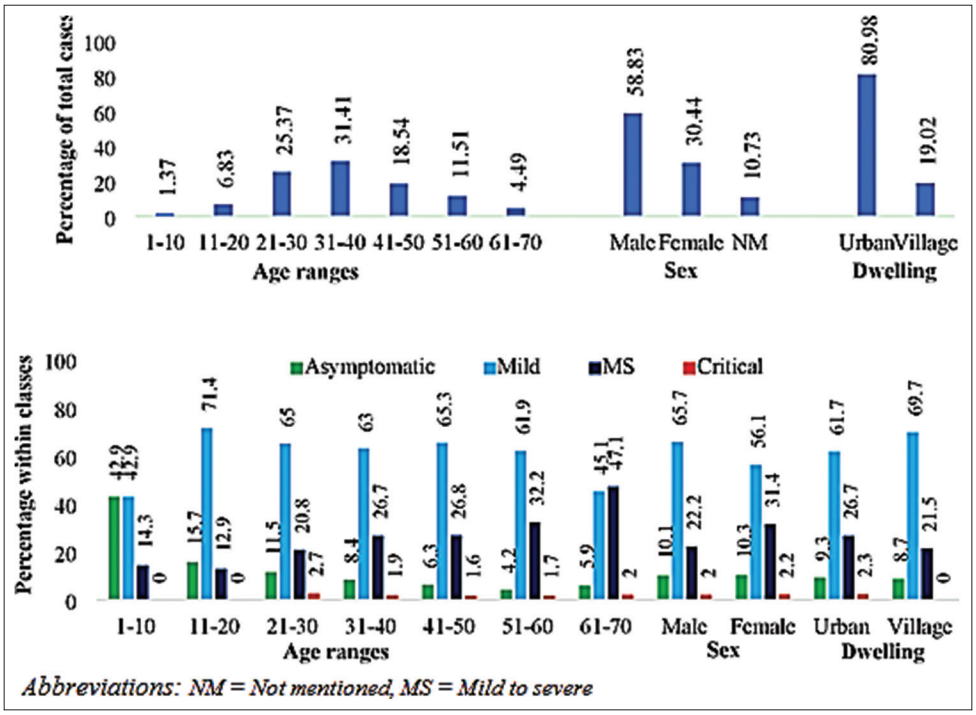
Supplementary



SI Figure 1: Age distribution (%) for the symptomatic status of the COVID-19 patients, (A) Percentages of symptomatic status, (B) Percentages of total cases

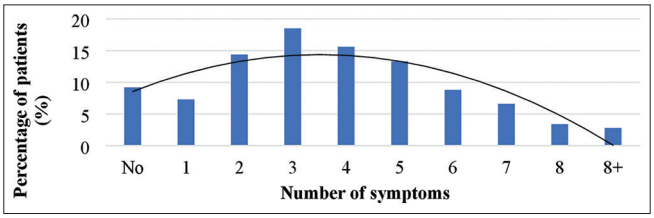
SI Table 1: Prevalent symptoms for age groups

Age ranges	N	Fever	Cough	Fatigue	No taste/smell	Sneezing	Sore throat	BPF	ROL	Most prevalent symptoms
01-10	12	58.3%	16.7%	33.3%	8.3%	16.7%	8.3%	8.3%	0.0%	Fever>Fatigue>Cough>Sneezing
11-20	70	77.1%	58.6%	25.7%	48.6%	10.0%	27.1%	25.7%	7.1%	Fever>Cough>No taste/ smell>Sore throat
21-30	260	80.4%	54.2%	38.5%	58.1%	16.2%	30.8%	33.1%	1.9%	Fever>Cough>No taste/ smell>Fatigue
31-40	322	82.6%	59.3%	39.4%	57.1%	20.8%	29.8%	38.8%	5.0%	Fever>Cough>No test/ smell>Fatigue
41-50	190	91.1%	57.9%	40.5%	50.0%	12.1%	30.5%	33.2%	6.3%	
51-60	118	88.1%	65.3%	44.9%	60.2%	13.6%	37.3%	44.9%	9.3%	
61-70	46	87.0%	82.6%	45.7%	65.2%	17.4%	43.5%	43.5%	17.4%	
70+	5	80.0%	40.0%	60.0%	0.0%	40.0%	40.0%	20.0%	0.0%	Fever>Fatigue>Cough>Sore throat
Male	603	83.4%	55.7%	34.8%	52.1%	20.1%	27.2%	35.2%	6.1%	Fever>Cough>No test/ smell>BPF
Female	312	78.2%	53.5%	47.4%	50.3%	12.5%	33.7%	41.0%	4.5%	Fever>Cough>No test/ smell>Fatigue
NM	110	100.0%	90.9%	40.9%	88.2%	7.3%	46.4%	24.5%	2.7%	Fever > Cough > No test/smell > Sore throat

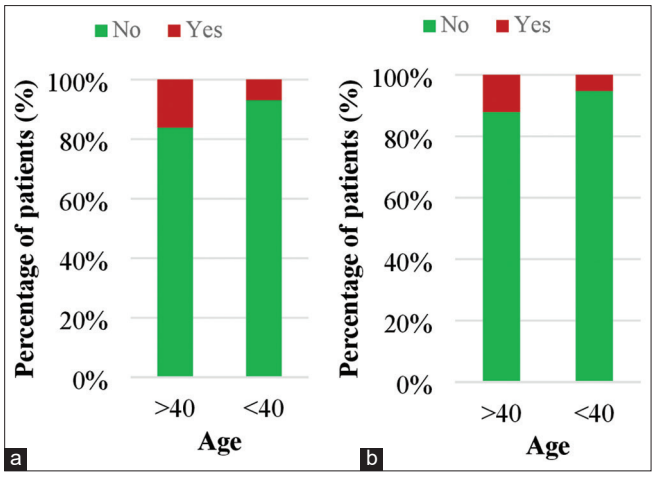
Abbreviations: BPF=Body pain with fever, ROL=Reduction in oxygen level, NM=Not mentioned

SI Table 2: Comorbidity distribution against sex

Comorbid patient			
	Total	**Comorbid**	**Non-comorbid**
Male	603	262 (43.4%)	341 (56.5%)
Female	312	159 (51%)	153 (49%)
Not mentioned	110	46 (41.8%)	64 (58.2%)
Total	1025	467 (45.6%)	558 (54.4%)
Hospitalization of comorbid patients against sex			
	Hospitalized	**Comorbid**	**Non-comorbid**
Male	50	32 (64%)	18 (36%)
Female	42	23 (54.8%)	19 (45.2%)



SI Figure 2: Symptoms experienced by patients



SI Figure 3: Hospitalization history with respect to age, sex associated with comorbidity status (a) With comorbidity, (b) Without comorbidity

SI Table 3: Test of significant dependence of symptomatic case and duration of recovery

	Levene's Test for Equality of Variances		t-test for Equality of Means				
	F	Sig.	t	df	Sig. (2-tailed)	MD	SE
Test for symptomatic case							
Sex	0.018	0.894	-0.067	913	0.947	-0.001	0.021
Comorbidity	32.480	<.001	-2.860	1016.069	0.004	-0.050	0.018
Habitation	0.239	0.625	0.243	1023	0.808	0.006	0.023
DM	41.752	<.001	-2.977	1023	0.003	-0.076	0.025
HC	4.615	0.032	-1.036	1023	0.301	-0.034	0.033
Asthma	3.368	0.067	0.832	69.300	0.408	0.036	0.043
HD	0.223	0.637	0.225	40.686	0.823	0.011	0.050
CKD	7.113	0.008	-1.197	1023	0.232	-0.093	0.078
CVD	0.063	0.801	-0.127	36.534	0.900	-0.006	0.049
HTN	45.356	<.001	-3.112	1023	0.002	-0.075	0.024
Allergy	0.289	0.591	-0.281	26.496	0.781	-0.015	0.054
Medicines	0.288	0.591	-10.863	1023	<.001	-0.83402	0.07678
Antipyretics	1.081	0.299	-10.576	1023	<.001	-0.80815	0.07641
Antivirals	2.825	0.093	-5.218	1023	<.001	-0.26518	0.05082
Antimalarials	1.015	0.314	-4.509	1023	<.001	-0.22632	0.05020
Antihistaminic	0.944	0.331	-6.237	1023	<.001	-0.33029	0.05296
Antibiotics	0.677	0.411	-10.669	1023	<.001	-0.75123	0.07041
Steroids	1.015	0.314	-4.509	1023	<.001	-0.22632	0.05020
Test for hospitalization							
Sex	23.943	<.001	2.471	913	0.014	0.052	0.021
Comorbidity	44.608	<.001	-3.299	1023	0.001	-0.060	0.018
Habitation	8.759	0.003	-1.438	1023	0.151	-0.033	0.023
DM	72.766	<.001	-4.619	1023	<.001	-0.118	0.026
HC	0.377	0.539	0.316	98.517	0.753	0.010	0.032
Asthma	10.966	0.001	-1.776	1023	0.076	-0.067	0.038

	Levene's Test for Equality of Variances		t-test for Equality of Means				
	F	Sig.	t	df	Sig. (2-tailed)	MD	SE
HD	3.791	0.052	1.191	43.367	0.240	0.044	0.037
CKD	27.336	<.001	-4.367	1023	<.001	-0.340	0.078
CVD	39.201	<.001	-3.995	1023	<.001	-0.199	0.050
HTN	36.369	<.001	-3.171	1023	0.002	-0.077	0.024
Allergy	4.365	0.037	0.978	1023	0.328	0.057	0.058
Test for severity							
Sex	32.222	<.001	3.046	913	0.002	0.094	0.031
Comorbidity	160.791	<.001	-6.591	1023	<.001	-0.181	0.027
Habitation	21.779	<.001	-2.110	1023	0.035	-0.075	0.036
DM	39.170	<.001	-4.369	1023	<.001	-0.172	0.039
HC	24.243	<.001	-4.150	1023	<.001	-0.211	0.051
Asthma	15.480	<.001	-2.993	1023	0.003	-0.172	0.058
HD	10.642	0.001	-3.017	1023	0.003	-0.219	0.073
CKD	2.902	0.089	-1.120	13.273	0.282	-0.155	0.138
CVD	8.058	0.005	-4.004	1023	<.001	-0.306	0.076
HTN	14.986	<.001	-2.212	1023	0.027	-0.083	0.037
Allergy	0.026	0.872	0.078	26.289	0.938	0.007	0.090
Test for duration of recovery							

Sex	0.001	0.979	-1.361	654.312	0.174	-0.773	0.568
Comorbidity	18.961	<.001	-3.984	904	<.001	-2.018	0.506
Habitation	9.261	0.002	-1.256	904	0.210	-0.802	0.639
DM	2.080	0.150	-1.081	159.266	0.281	-0.942	0.871
HC	0.921	0.337	-2.345	89.562	0.021	-2.205	0.940
Asthma	3.783	0.052	-1.185	60.975	0.241	-1.499	1.265
HD	0.583	0.445	-1.633	40.838	0.110	-1.570	0.961
CKD	0.047	0.828	-1.972	12.391	0.071	-4.005	2.031
CVD	0.179	0.672	-1.403	35.387	0.169	-1.960	1.397
	Levene's Test for Equality of Variances		**t-test for Equality of Means**				
	F	**Sig.**	**t**	**df**	**Sig. (2-tailed)**	**MD**	**SE**
HTN	7.047	0.008	-2.149	904	0.032	-1.450	0.675
Allergy	2.292	0.130	-0.431	22.512	0.671	-1.024	2.375
Medicines	0.667	0.414	-1.170	1023	0.242	-1.35228	1.15606
Antipyretics	0.845	0.358	-1.206	903	0.228	-1.38020	1.14431
Antivirals	5.710	0.017	-2.356	294.954	0.019	-1.28558	0.54574
Antimalarials	6.131	0.013	-2.293	312.811	0.023	-1.23389	0.53815
Antihistaminic	7.857	0.005	-2.991	256.200	0.003	-1.61137	0.53868
Antibiotics	0.916	0.339	-1.234	903	0.218	-1.26900	1.02851
Steroids	6.131	0.013	-2.293	312.811	0.023	-1.23389	0.53815
Symptoms	36.458	<.001	-3.549	92	0.001	-7.19872	2.02855
Severity	14.222	<.001	-4.027	904	<.001	-2.242	0.557

DM=Diabetes mellitus, HTN=Hypertension, CVD=Cardiovascular disease, HC=Hypercholesterolemia, RA=Rheumatoid arthritis, HD=Hepatic disorder, CKD=Chronic kidney disease
Note: P<0.05 is significant at two-tailed test

SI Table 4: Different medicine used during the recovery of Covid-19 patients

	Antipyretics	**Antivirals**	**Antimalarials**	**Antihistaminics**	**Antibiotics**	**Steroids**
Antipyretics		851	844	870	949	844
		83.0%`	82.3%	84.9%	92.7%	82.3%
Antivirals	851		844	847	850	844
	83.0%		82.3%	82.7%	82.9%	82.3%
Antimalarials	844	844		844	844	844
	82.3%	82.3%		82.3%	82.3%	82.3%
Antihistaminics	870	847	844		869	844
	84.9%	82.7%	82.3%		84.8%	82.3%
Antibiotics	949	850	844	869		844
	92.7%	82.9%	82.3%	84.8%		82.3%
Steroids	844	844	844	844	844	
	82.3%	82.3%	82.3%	82.3%	82.3%	

Remarks: 844 patients used all the medicines. 962 patients took antipyretic medicine along with other medicines where 11 of them taken only it. Combination of antipyretic, antibiotic, antiviral was highly used (850 cases).77 patients taken only the combination of antipyretic and antibiotic medicines. Those who used steroid, antimalarial and antiviral medicine also took other medicines. Not surprising that only the symptomatic cases had the medication history (p<0.001). Briefly symptomatic cases had the history of taking antipyretic (p<0.001), antiviral (p<0.001), antimalarial (p<0.001), antibiotic (p<0.001), antihistaminic (p<0.001) and steroid (p<0.001) drugs. The use of antiviral (p=0.019), antimalarial (p=0.023), antihistaminic (p=0.003) and steroid (p=0.023) drugs was found to have positive impact in reducing the time of recovery.

SI Table 5: Pearson Chi-Square tests for degree of severity

	Value	df	Asymptotic Significance (2-sided)	Approximate Significance
Degree of severity				
Sex				
Pearson Chi-Square	9.306[a]	2	0.010	
Likelihood Ratio	9.174	2	0.010	
Phi	0.095			0.010
Habitation				
Pearson Chi-Square	5.223[b]	1	0.022	
Likelihood Ratio	5.456	1	0.020	
Phi	0.071			0.022
Comorbidity				
Pearson Chi-Square	41.756[c]	1	<.001	
Likelihood Ratio	41.827	1	<.001	
Phi	0.202			<.001
Hospitalization admission				
Sex				
Pearson Chi-Square	11.239[d]	2	0.004	
Likelihood Ratio	11.777	2	0.003	
Phi	0.105			0.004
Habitation				
Pearson Chi-Square	2.927e	1	.087	
Likelihood Ratio	3.210	1	.073	
Phi	053			
Comorbidity				
Pearson Chi-Square	10.793[f]	1	0.001	
Likelihood Ratio	10.776	1	0.001	
Phi	0.103			0.001

[a] 0 cells (0.0%) have expected count less than 5. The minimum expected count is 30.37
[b] 0 cells (0.0%) have expected count less than 5. The minimum expected count is 53.84
[c] 0 cells (0.0%) have expected count less than 5. The minimum expected count is 128.94
[d] 0 cells (0.0%) have expected count less than 5. The minimum expected count is 10.30
[e] 0 cells (0.0%) have expected count less than 5. The minimum expected count is 18.26
[f] 0 cells (0.0%) have expected count less than 5. The minimum expected count is 43.74

SI Table 6: (a). t-test statistics for comorbid and non-comorbid patients recovery duration

	Comorbidity	N	Mean	Std. Deviation	Std. Error Mean
Recovery	No	488	17.51	6.10	0.275
	Yes	418	19.52	9.06	0.44

SI Table 6: (b). t-test for the difference in comorbid and non-comorbid patients recovery duration

	Levene's Test for Equality of Variances		t-test for Equality of Means						
	. F	Sig	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper
Recovery									
Equal variances assumed	18.961	0.075	-3.984	904	<.001	-2.01778	0.50641	-3.01165	-1.02390
Equal variances not assumed			-3.869	709.023	<.001	-2.01778	0.52157	-3.04178	-0.99377

SI Table 7: Forward regression models for identifying best fit

	Chi-square	df	Sig.	-2 log likelyhood
Degree of severity (R^2=0.79)				
Step 1				
Step	41.827	1	<.001	1166.094
Block	41.827	1	<.001	
Model	41.827	1	<.001	
Step 2				
Step	7.195	2	0.027	1158.899
Block	49.022	3	<.001	
Model	49.022	3	<.001	
Step 3				
Step	4.650	1	0.031	1154.248
Block	53.673	4	<.001	
Model	53.673	4	<.001	
Hospital admission (R^2=0.82)				
Step 1				
Step	102.822	69	0.005	534.567
Block	102.822	69	0.005	
Model	102.822	69	0.005	
Step 2				
Step	22.698	2	<.001	511.869
Block	125.520	71	<.001	
Model	125.520	71	<.001	

SI Table 8: (a). Influence of indicators from forward binary logistic regression analysis for degree of severity

	B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP (B)	
							Lower	Upper
Step 1[a]								
Comorbidity	0.915	0.144	40.615	1	<.001	2.497	1.885	3.309
Constant	-2.342	0.235	99.632	1	<.001	0.096		
Step 2[b]								
Sex			7.229	2	0.027			
Sex (1)	0.412	0.156	6.962	1	0.008	1.510	1.112	2.051
Sex (2)	0.275	0.235	1.371	1	0.242	1.317	0.831	2.089
Comorbidity	0.898	0.144	38.767	1	<.001	2.456	1.851	3.258
Constant	-2.481	0.243	103.863	1	<.001	0.084		
Step 3[c]								
Sex			7.326	2	0.026			
Sex (1)	0.389	0.157	6.140	1	0.013	1.475	1.085	2.006
Sex (2)	0.397	0.243	2.664	1	0.103	1.488	0.923	2.397
Habitation (1)	0.427	0.203	4.444	1	0.035	1.533	1.030	2.280
Comorbidity	0.892	0.145	38.079	1	<.001	2.441	1.838	3.240
Constant	-2.829	0.298	90.258	1	<.001	0.059		

a. Variable (s) entered on step 1: Comorbidity.
b. Variable (s) entered on step 2: Sex.
c. Variable (s) entered on step 3: Habitation.

SI Table 8: (b). Influence of indicators from forward binary logistic regression analysis for hospital admission

	B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for EXP (B)	
							Lower	Upper
Step 1[a]								
Comorbidity (1)	0.711	0.220	10.459	1	<.001	2.036	1.323	3.133
Constant	-2.645	0.170	241.658	1	.<.001	0.071		
Step 2[b]								
Sex			9.287	2	0.010			
Sex (1)	0.498	0.224	4.956	1	0.026	1.645	1.061	2.550
Sex (2)	-0.868	0.531	2.667	1	0.102	0.420	0.148	1.190
Comorbidity (1)	0.672	0.221	9.217	1	0.002	1.958	1.269	3.021
Constant	-2.742	0.195	197.358	1	<.001	0.064		

a. Variable (s) entered on step 1: Comorbidity.
b. Variable (s) entered on step 2: Sex.