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Clinical characteristics and outcomes of COVID-19: Experience at a major tertiary care center in Pakistan

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Coronavirus Pandemic

Clinical characteristics and outcomes of COVID-19: Experience at a major tertiary care center in Pakistan

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Abstract

Introduction: Limited data exist on clinical characteristics and outcomes of hospitalized COVID-19 patients in low-middle income countries. We aimed to describe the clinical spectrum and outcomes of hospitalized COVID-19 patients at a tertiary-care center in Karachi, Pakistan.

Methodology: We conducted an observational study of adult COVID-19 patients hospitalized between February-June 2020. Patients with a discharge diagnosis of COVID-19 and PCR positivity were included. We created logistic regression models to understand association of clinical characteristics with illness severity and in-hospital mortality.

Results: The study population comprised 445 patients [67% males, median age 53 (IQR 40-64) years]. Majority of patients (N = 268; 60%) had ≥ 1 co-morbid [37.5% hypertension, 36.4% diabetes]. In-hospital mortality was 13%. Age ≥ 60 (aOR] =1.92; 95 %CI = 1.23-3.03), shortness of breath (aOR=4.43; 95% CI=2.73-7.22), CRP ≥150mg/L (aOR:1.77; 95% CI=1.09-2.85), LDH ≥ 500 I.U/L (aOR:1.98; 95% CI=1.25-3.16), Neutrophil-to-Lymphocyte ratio (NLR) ≥5 (aOR:2.80; 95%CI = 1.77-4.42) and increase in serum creatinine (aOR:1.32; 95%CI=1.07-1.61) were independently associated with disease severity. Septic shock (aOR: 13.27; 95% CI=3.78-46.65), age ≥ 60 (aOR: 3.26; 95% CI=1.07-9.89), Ferritin ≥ 1500ng/ml (aOR: 3.78; 95% CI=1.21-11.8), NLR ≥ 5 (aOR: 4.04; 95% CI=1.14-14.35) and acute kidney injury (aOR: 5.52; 95% CI=1.78-17.06) were independent predictors of in-hospital mortality.

Conclusions: We found multiple predictors to be independently associated with in-hospital mortality, except diabetes and gender. Compared to reports from other countries, the in-hospital mortality among COVID-19 patients was lower, despite a high burden of co-morbidities. Further research is required to explore reasons behind this dichotomy.

Key words: COVID-19; Mortality; Pakistan; low-middle income country.

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Introduction

Rapidly evolving data on COVID-19 from across the globe show that its disease severity and mortality are heterogeneous. The proportion of severely ill patients presenting to the hospital and in-hospital mortality of COVID-19 has been invariably high. Initial reports from the United Kingdom showed an in-hospital mortality was 26% in the 17% of patients admitted with severe to critical disease [1]. Similarly in the United States up to 25% of hospitalized patients were critically ill and the in-hospital mortality ranged from 21% to 25% [2,3]. These data cannot be imputed or used as a surrogate for low middle-income countries due to the inherent differences in population health care access, immunity and, high background burden of communicable and non-communicable diseases. Data on hospitalized patients from developing countries are now being reported from tertiary care centers in the region. A study from Bangladesh has reported a 28-day mortality of 2.5% with a greater risk of death among elderly with co-morbid conditions [4]. Studies from India have shown that up to 14% of symptomatic patients developed a severe illness and the in-hospital mortality ranged was 4.5 to 5% with similar risk factors as those reported from Bangladesh [5,6]. A Single-center study from Egypt reported a greater incidence of hospitalization and severity in patients with an age of greater than 50 years [7]. Limited data have been reported from small studies in Pakistan largely confined to intensive care settings [8,9]. An elaborate understanding of clinical characteristics and outcomes of hospitalized COVID-19 patients in low-middle income countries (LMICs) represents an important knowledge gap given the heterogeneity of data from these countries [10]. Bridging this knowledge gap is necessary for increasing our understanding of the risks

and designing interventions for managing the most susceptible patients. To address this gap we evaluated clinical, biochemical, and radiological features and outcomes of COVID-19 in a larger cohort of 445 patients at an academic medical center in Karachi with a dedicated facility for COVID-19.

Methodology

Study population and Design

We conducted an observational study of adult COVID-19 patients hospitalized at the dedicated COVID-19 facility at the Aga Khan University Hospital between February 26 and June 10, 2020. We included all adult patients (≥ 18 years old) who had a discharge diagnosis of COVID-19 and had a positive PCR for COVID-19 RNA.

Data collection

We first curated a list of all patients hospitalized with a discharge diagnosis and positive PCR test for COVID-19 through the Hospital information management system. A detailed chart review was then conducted to extract demographics, clinical characteristics, outcomes, and treatment details of confirmed COVID-19 patients including underlying co-morbidities, laboratory and radiological investigations, and complications during hospitalization using a structured proforma. Patients were stratified based on the severity of illness which was defined as follows: a) Asymptomatic/Mild Illness: Patients who are either symptom-free or symptomatic COVID-19 patients who do not have hypoxia; b) Moderate Illness: Patients with evidence of lower respiratory disease during clinical assessment or imaging and who have a saturation of oxygen (SpO2) ≥90% on room air; c) Severe/Critical Illness: Patients with any of the following: SpO2 < 90% on room air, PaO2/FiO2 < 300 mm Hg, respiratory frequency >30 breaths/min, or > 50% infiltrates on chest radiograph and/or any of complications including respiratory failure/ARDS, septic shock, and/or multiple organ dysfunction.

Diagnosis of COVID-19

All included patients underwent nasopharyngeal swabs which were processed for detection of SARS-Cov-2 virus by real-time reverse transcriptase polymerase chain reaction (RT-PCR) using the WHO protocol for the 2019- nCoV RT-PCR assay in March 2020. Specimens in May were tested using the Cobas® SARS-CoV-2 RT-PCR assay (Roche Diagnostics, Indianapolis, IN, USA). A radiological diagnosis of pneumonia was made by evaluation of infiltrates observed on chest radiographs and/or CT chest. A multidisciplinary team of doctors including infectious disease consultants, pulmonologists, and intensivists was involved in the identification of cases and their management.

Statistical analysis

Descriptive analysis was performed for demographic features with mean and standard deviation or median with interquartile range (IQR) reported for quantitative variables such as age and lengths of hospital stay as appropriate. Frequencies (percentage) for qualitative variables such as gender, co-morbid conditions, mortality, and complications. Continuous variables were also transformed into categorical variables for further analysis as indicated. $\chi 2$ test of independence or Fischer exact test was performed for categorical variables such as comparison of those with COVID-19 who died with those who were discharged. We created univariable and multivariable logistic regression models to understand the association of risk factors associated with illness severity of COVID-19, (mild, moderate, and severe/critical). To identify factors independently associated with death in COVID-19 infection we created a stepwise multivariable logistic regression model. The model included variables found to be significant on univariable analysis and those deemed of clinical relevance. Unadjusted and adjusted odds ratios were reported. We included interaction terms to understand the interaction between age and gender. Significance was set at a value ≤0.05. STATA Version 12.1was used for data analysis.

Ethics approval

This study received approval from the Aga Khan University Ethics Review Committee of the hospital (ERC reference number: 2020-3650-11773). The data was collected from hospital records and the requirement for informed consent was waived by the hospital ethical review committee as data was anonymized and no personal identifiers were collected.

Results

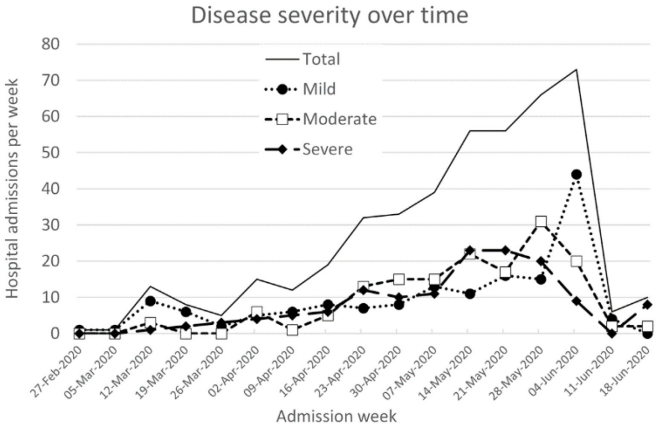
Demographics, Clinical characteristics, and course of the disease

Of a total of 11,393 adult patients admitted to the Aga Khan University Hospital between Feb 26, 2020, and June 10, 2020, 445 (3.9%) patients were diagnosed with COVID-19 based on RT-PCR positivity for SARS-CoV-2. Most of the hospitalized COVID-19 patients were male (298, 67%). The median age of the cohort was 53 years (IQR 40 – 64 years). Age was

further categorized into groups: 11.7% (N = 52) of the patients were between 18 and 29 years of age, 12.8% (N = 57) between 30 and 39 years, 18.4% (N = 84) between 40 and 49 years, 23.1% (N = 103) between 50 and 59 years, 18.8% (N = 84) between 60 and 69 years,11.5% (N = 51) between 70 and 79 years, and 3.6% (N = 16) of the patients were greater than 80 years of age.

A total of 55 patients were (12.4%) asymptomatic and 137 (30.8%) had severe/critical disease. Most (268; 60.2%) patients had at least one or more than one co-morbidity, of which hypertension was the most common (37.5%) followed by diabetes (36.4%). Among symptomatic patients (n= 390, 87.6%), the most common symptom was fever (80%) followed by cough (61.3%) and shortness of breath (61.0%). The median duration of illness prior to presentation was 7 days (IQR 3-10) and was longer with worsening severity of illness (median of 3 days in mild, 7 days in moderate and severe each). Admissions peaked in May and then steadily reduced over time. The proportion of patients with severe disease increased with time; in March, 25% of admitted patients were severely ill and in May 34% of admitted patients had severe disease. Despite the increasing severity, the proportion of in-hospital mortality increased in May and started to decline in June (Figure 1). The median C-reactive protein (CRP) level was 83.3 mg/L (IQR: 27.8 -178.9) and the median ferritin level was 551 ng/ml (IQR: 254.1-1258.3). Overall, 124 (27.9%) required non-invasive ventilation (NIV) and 64 (14.5%) required invasive positive pressure (IPPV) ventilation. Chest X-rays were performed in 432 patients (97%). Chest X-rays were normal in 21.57% of patients. Unilateral involvement was seen less frequently as compared to bilateral disease (7.7% vs 66% respectively). Treatment received

Figure 1. Weekly time plot of hospital admissions according to severity of disease, showing predominance of mild cases in week 2 and 3 after the first reported case, with subsequent rise of severe cases peaking at week 11 and 12. At week 14, a week before the sharp decline over the peak of the curve, severe cases decline and there are predominantly mild cases.



varied as the protocols changed with chloroquine use dropping from 2.25% of patients to zero between February and April. Similarly, hydroxychloroquine was given to 31% of patients overall with use declining from 47% to 2.1% between April and June. Among antivirals; nine patients received oseltamivir and two patients received lopinavir/ritonavir. Systemic steroids and intravenous tocilizumab were administered to moderate to severely ill patients with hypoxia and laboratory evidence of hyperinflammation. Overall, 56% of the patients (N=249) received systemic steroids and 19.3% (N=86) received intravenous tocilizumab during hospitalization. Sixty-eight patients (15%) required ICU admission. Septic shock was seen in 62 (14%) of the cases while 44 (9.9%) presented in multi-organ dysfunction. Acute kidney injury was seen in 96 (21.6%) and 46 (10.3%) patients presented with a

Table 1. Comparison of mild, moderate and severe COVID-19 patients admitted at tertiary care center in Karachi, Pakistan.

Variables	All (N = 445)	Mild (N = 156)	Moderate (N = 152)	Severe (N = 137)	p-value
Age* (mean ± SD)	51.6 ± 16.1	42.3 ± 16.2	54.0 ± 12.7	59.4 ± 14.1	< 0.001
Gender*					
Male	298 (67%)	86 (55.1%)	108 (71.1%)	105 (76.6%)	< 0.001
Female	147 (33%)	70 (44.9%)	44 (28.9%)	32 (23.4%)	
Duration of illness* [median (IQR) days]	7 (3-10)	3 (0-7)	7 (5-10)	7 (5-10)	< 0 .001
Co-morbids					
Diabetes*	162 (36.4%)	28 (17.9%)	70 (46.1%)	64 (46.7%)	< 0.001
Hypertension*	167 (37.5%)	30 (19.2%)	65 (42.8%)	72 (52.6%)	< 0.001
Ischemic heart disease*	74 (16.6%)	10 (6.4%)	25 (16.4%)	39 (28.5%)	< 0.001
Chronic kidney disease*	31 (7%)	2 (1.3%)	13 (8.6%)	16 (11.7%)	0.001
Malignancy	22 (4.9%)	8 (5.1%)	5 (3.3%)	9 (6.6%)	0.601
Stroke*	10 (2.2%)	0 (0%)	3 (2%)	7 (5.1%)	0.007
Chronic liver disease	8 (1.8%)	4 (2.6%)	1 (0.7%)	3 (2.2%)	0.739

Table 1 (continued). Comparison of mild, moderate and severe COVID-19 patients admitted at tertiary care center in Karachi, Pakistan.

Variables	All (N = 445)	Mild (N = 156)	Moderate (N = 152)	Severe (N = 137)	p-value
Symptoms					
Fever*	312 (70.1%)	83 (53.2%)	126 (82.9%)	103 (75.2%)	< 0.001
Cough*	239 (53.7%)	56 (35.9%)	103 (67.8%)	80 (58.4%)	< 0.001
Shortness of breath*	238 (53.5%)	24 (15.4%)	100 (65.8%)	114 (83.2%)	<0 .001
Sore throat*	48 (10.8%)	22 (14.1%)	18 (11.8%)	8 (5.8%)	0.028
Myalgias	52 (11.7%)	21 (13.5%)	16 (10.5%)	15 (10.9%)	0.736
Radiologic findings					
Normal*	96 (21.6%)	93 (59.6%)	3 (2%)	1 (0.7%)	< 0.001
Bilateral involvement*	291 (65.4%)	32 (20.5%)	133 (87.5%)	126 (92%)	< 0.001
Unilateral involvement	34 (7.6%)	10 (6.4%)	17 (11.2%)	7 (5.1%)	0.733
Patchy infiltrates*	293 (65.8%)	33 (21.2%)	137 (90.1%)	123 (89.8%)	< 0.001
Multilobar involvement*	178 (40%)	14 (9%)	85 (55.9%)	79 (57.7%)	< 0.001
Consolidation*	48 (10.8%)	7 (4.5%)	18 (11.8%)	23 (16.8%)	0.001
CURB score* [median (IQR)]	1 (0-2)	0 (0)	1 (0-1)	2 (1-3)	< 0.001
Laboratory Investigations					
C-Reactive Protein* <150 mg/L	252 (56.6%)	96 (61.5%)	105 (69.1%)	51 (37.2%)	<0.001
C-Reactive Protein >=150 mg/L	193 (43.4%)	60 (38.5%)	47 (30.9%)	86 (62.8%)	
LDH* <500 IU/L	235 (52.8%)	81 (51.9%)	109 (71.7%)	45 (32.8%)	0.003
LDH>=500 IU/L	210 (47.2%)	75 (48.1%)	43 (28.3%)	92 (67.2%)	
Neutrophil to lymphocyte ratio* <5	255 (57.3%)	118 (75.6%)	95 (62.5%)	42 (30.7%)	<0.001
Neutrophil to lymphocyte ratio >=5	190 (42.7%)	38 (24.4%)	57 (37.5%)	95 (69.3%)	
Ferritin <1500 ng/ml	249 (56%)	84 (53.8%)	104 (68.4%)	61 (44.5%)	0.162
Ferritin>=1500 ng/ml	196 (44%)	72 (46.2%)	48 (31.6%)	76 (55.5%)	
Type of Ward					
ICU Admission*	68 (15.3%)	0 (0%)	1 (0.7%)	67 (48.9%)	< 0.001
SCU Admission*	148 (33.3%)	12 (7.7%)	75 (49.3%)	61 (44.5%)	< 0.001
Ward admission*	223 (50.1%)	141 (90.4%)	76 (50%)	6 (4.4%)[i]	< 0.001
Treatment					
Non-invasive ventilation*	124 (27.9%)	0 (0%)	35 (23%)	89 (65%)	< 0.001
Invasive ventilation*	64 (14.4%)	0 (0%)	0 (0%)	64 (46.7%)	< 0.001
Oxygen support*	278 (62.5%)	8 (5.1%)[ii]	135 (88.8%)	135 (98.5%)	< 0.001
Antibiotics*	236 (53%)	25 (16%)	86 (56.6%)	125 (91.2%)	< 0.001
Azithromycin*	164 (36.9%)	16 (10.3%)	68 (44.7%)	80 (58.4%)	< 0.001
Hydroxychloroquine*	139 (31.2%)	11 (7.1%)	67 (44.1%)	61 (44.5%)	< 0.001
Chloroquine	10 (2.2%)	1 (0.6%)	4 (2.6%)	5 (3.6%)	0.093
Tocilizumab*	86 (19.3%)	0 (0%)	21 (13.8%)	64 (46.7%)	< 0.001
Oseltamivir*	9 (2%)	0 (0%)	3 (2%)	6 (4.4%)	0.014
Lopinavir/Ritonavir	3 (0.7%)	0 (0%)	1 (0.7%)	2 (1.5%)	0.161
Systemic steroids*	249 (56%)	6 (3.8%)[iii]	120 (78.9%)	123 (89.8%)	< 0.001
Vasopressors*	59 (13.3%)	0 (0%)	1 (0.7%)	58 (42.3%)	< 0.001
Complications					
ARDS*	122 (27.4%)	0 (0%)	19 (12.5%)	103 (75.2%)	< 0.001
Septic Shock*	62 (13.9%)	0 (0%)	0 (0%)	62 (45.3%)	< 0.001
MODS*	44 (9.9%)	0 (0%)	3 (2%)	41 (29.9%)	< 0.001
Nosocomial Infection*	59 (13.3%)	1 (0.6%)	10 (6.6%)	48 (35%)	< 0.001
AKI*	96 (21.6%)	5 (3.2%)	21 (13.8%)	70 (51.1%)	< 0.001
NSTEMI*	46 (10.3%)	1 (0.6%)	9 (5.9%)	36 (26.3%)	< 0.001
Length of stay* [median (IQR) days	5 (3-9)	3 (2-5)	6 (4-9)	8 (5-14)	< 0.001
Dead*	58 (13%)	0 (0%)	3 (2%)	55 (40.1%)	< 0.001
Discharged	360 (80.9%)	144 (92.3%)	142 (93.4%)	74 (54%)	
Left against medical advice (LAMA)	27 (6.1%)	12 (7.7%)	7 (4.6%)	8 (5.8%)	

* significant at p-value < 0.05; i:These were patients with severe disease admitted for comfort care; ii: This includes patient who had polytrauma, hematemesis, gastrointestinal bleed etc. who were incidentally diagnosed with COVID-19; iii:These were varied, one with underlying malignancy, one with penumoperitoneum who was found on preop screening, a couple had raised ferritin only.

ICU mortality was 58.8% (40/68). A total of 58 patients died with an overall mortality rate of 13%. (Table 1).

Comparison of Severe, moderate, and mild disease

In all, 35% of patients had asymptomatic/mild disease, 34% moderate, and 30% had severe/critical disease on admission. Compared with patients with asymptomatic/mild and moderate disease, patients with severe disease were older, (severe disease: mean 59 years vs mild disease 42 years); and were likely to have co-morbidities such as diabetes, hypertension, and ischemic heart disease (*p*-value < 0.001).

A greater proportion of patients with severe disease had shortness of breath (83%) on presentation. Chest radiographic with bilateral peripheral opacities were seen in majority of the patients with moderate (87.5%) and severe disease (92%) whereas most of the mildly diseased patients (60%) had a normal chest x-ray. Patients with greater severity of illness had significantly higher median CRP, ferritin, LDH, and D-Dimer values as well as a higher mean neutrophil to lymphocyte ratio compared to those with mild and moderate disease (p-value < 0.001). Hydroxychloroquine was given to 44% patients with moderate and 44% patients with severe disease respectively. Intravenous steroids were used in majority of the patients with moderate and severe disease (79% and 90% respectively). Intravenous Tocilizumab was administered to 86 (19.3%) cases and predominantly among those with severe disease (47.4%). Antibiotic use was common in severe disease with 91% receiving any antibiotics as opposed to16.5% of the mild and 57% of moderate cases.

Associations of Severity of Illness

Ordinal logistic regression was performed to determine predictors of severity (Table 2). Multivariable ordinal regression analysis revealed that the risk of having severe disease was 1.92 (95% CI: 1.23 -3.03) times higher in patients with age ≥ 60 years of age when compared with patients < 60 years. Presence of shortness of breath at presentation (OR = 4.43; 95% CI: 2.73-7.22) and presence of bilateral peripheral opacities on chest radiograph was associated with greater severity of illness (OR=5.81; 95% CI: 2.90-11.62). Among laboratory investigations done on admission; the risk of greater severity of illness was associated with CRP ≥ to 150mg/L (OR=1.77; 95% CI: 1.10-2.85), LDH ≥ 500 I.U/L (OR=1.98; 95% CI: 1.25-3.16), Neutrophil to Lymphocyte ratio ≥ 5 (OR = 2.80; 95% CI: 1.77-4.42) and a unit increase in serum creatinine level in mg/dl (OR=1.32; 95% CI: 1.07-1.61). None of the treatment modalities had any statistically significant impact on the severity of illness.

Factors associated with odds of death

Univariable predictors of death included older age, male sex, co-morbid conditions, and presence of complications such as septic shock, multi-organ dysfunction, acute kidney injury, myocardial infarction, and nosocomial infections (Table 3). Majority of the patients who died (69%) had been admitted to the ICU. There was only one death in the ward due to an underlying malignancy. All of the 17 patients who died in the High Dependency Units had a code status of was either Do-Not-Resuscitate (DNR) or comfort care due to an underlying terminal illness.

Table 2. Multivariable ordinal logistic regression for factors associated with level of severity.

Variable	Categories	OR	95% CI	p-value
Age	< 60 years (Ref)	1		
	> = 60 years	1.93	1.23-3.03	0.004
Shortness of breath	Absent (Ref)	1		
	Present	4.44	2.73-7.22	< 0.001
Bilateral chest radiographic findings	Absent (Ref)	1		
	Present	3.13	1.58- 6.17	0.001
Patchy infiltrates	Absent (Ref)	1		
	Present	5.81	2.90-11.6	< 0.001
C-Reactive Protein	< 150 (Ref)	1		
	> = 150	1.77	1.09-2.85	0.019
Lactate dehydrogenase	< 500(Ref)	1		
	> = 500	1.98	1.25-3.16	0.004
Neutrophil to lymphocyte ratio	< 5 (Ref)	1		
	> = 5	2.80	1.77-4.42	< 0.001
Creatinine* on admission		1.32	1.07-1.61	0.008

*per unit increase.

Table 3. Risk Factors associated with mortality.

Variables	Died (N = 58)	Recovered (N = 360)	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Age groups⁎⁎						
< 60 years (Ref)	23	257	1		1	
> = 60 years	35	103	3.79 (2.14-6.74)	< 0.001	3.26 (1.07-9.89)	0.037
Gender⁎						
Female (Ref)	11	130	1			
Male	47	230	2.42 (1.21-4.82)	0.012		
Co-morbids (present vs. not present)						
Diabetes⁎	28	124	1.78 (1.02-3.11)	0.044		
Hypertension⁎	31	124	2.18 (1.25-3.83)	0.006		
Ischemic heart disease⁎	20	50	3.26 (1.76-6.06)	< 0.001		
CKD⁎	12	17	5.26 (2.36-11.72)	< 0.001		
Malignancy⁎	7	12	3.98 (1.50-10.58)	0.006		
Radiologic findings (present vs. absent)						
Bilateral patchy infiltrates⁎	52	224	5.14 (2.15- 12.30)	< 0.001		
Laboratory investigations						
NLR⁎⁎						
< 5 (ref)	15	227	1			
> = 5	43	133	4.89 (2.62-9.14)	< 0.001	4.04 (1.14-14.35)	0.031
Ferritin ⁎⁎						
< 1500	18	217	1			
> = 1500	40	143	3.37 (1.86-6.11)	< 0.001	3.78 (1.21-11.8)	0.022
CRP⁎						
< 150 (ref)	23	216				
> = 150	35	144	2.28 (1.29-4.02)	0.004		
D-Dimer⁎						
< 1.5 (Ref)	14	206				
> = 1.5	44	154	4.20 (2.22-7.94)	< 0.001		
Creatinine⁎						
< = 1.2 (Ref)	19	264				
>1.2	39	96	5.64 (3.11-10.24)	< 0.001		
Type of admission unit						
ICU ⁎⁎	40	22	34.14 (16.9-69)	< 0.001	3.99 (1.22-13)	0.022
SCU	17	123	0.78 (0.43-1.46)	0.468		
Ward ⁎	1	211	0.012 (0.001-0.09)	< 0.001		
Treatment						
NIV⁎	34	83	4.72 (2.65- 8.42)	< 0.001		
Invasive ventilation⁎	36	22	25.14 (12.69-49.80)	< 0.001		
Oxygen support⁎	57	204	43.5 (5.97-318.24)	< 0.001		
Systemic steroids⁎	50	187	5.78 (2.67- 12.54)	< 0.001		
Tocilizumab⁎	19	66	2.21 (1.20-4.07)	0.01		
Complications present (vs absent)						
ARDS⁎	51	62	35.01 (15.1- 80.8)	< 0.001		
Septic Shock⁎⁎	46	10	134 (54.89- 327.9)	< 0.001	13.27 (3.78-46.65)	< 0.001
MODS⁎⁎	34	6	83.5 (31.96- 218.58)	< 0.001	8.60 (2.08-35.64)	0.003
Nosocomial Infection⁎	29	27	12.33 (6.46-23.55)	< 0.001		
AKI⁎⁎	47	43	31.39 (15.13-65.13)	< 0.001	5.52 (1.78-17.06)	0.003
NSTEMI⁎	21	21	9.16 (4.58-18.33)	< 0.001		
Median Length of stay in days⁎ (IQR)	8 (3-14)	5 (3-9)	1.04 (1.01-1.07)	0.016		

⁎ significant on univariable analysis at p-value<0.05; ⁎⁎ significant on multivariable analysis at p-value<0.05. CKD: Chronic kidney disease; CXR: Chest X-ray; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein; ICU: Intensive care unit; SCU: Special care unit; NIV: Non-invasive ventilation; ARDS: Acute respiratory distress syndrome; MODS: Multi-organ dysfunction Syndrome; AKI: Acute kidney injury; NSTEMI: Non-ST elevation myocardial infarction.

Presence of septic shock (AOR = 13.2; 95%CI: 3.78-46.65), multi-organ dysfunction (AOR= 8.6 (95%CI: 2.08- 35.64), acute kidney injury (AOR= 5.52; 95%CI: 1.78-17.06), admission to the ICU (AOR = 3.99; 95%CI: 1.22- 13), age ≥ 60 years (AOR= 3.25; 95%CI: 1.07 – 9.89) serum ferritin ≥ 1500ng/ml (AOR= 3.78; 95%CI: 1.21 -11.8) and NLR ≥ 5 (AOR = 4.04; 95%CI:1.14-14.35) were independently associated with mortality. None of the treatment options were found to have any significant benefit on mortality or length of stay. We tested for interactions between age, sex, and, diabetes but these were not significant.

Discussion

Our study highlights some of the differences in outcomes and severity seen in LMIC compared to previously reported studies. While our overall inpatient mortality was 13% and the patients had a significant burden of comorbid conditions, some of the "classic" risk factors for mortality were not found. While comorbid conditions were associated with mortality on univariable analysis, these were not found to be independent predictors of death on multivariable analysis. This is in contrast to most studies, which report an independent association of mortality with comorbid conditions such as diabetes, chronic kidney disease, and malignancy [11–15]. This is quite interesting considering the greater proportion of our cohort were diabetics (36% compared to 7.5 to 19% in China and 13 % in Italy). Few studies report a similar absence of statistically significant association between comorbid conditions and severity[16, 17]. Possibly, the baseline control of comorbid conditions may have influenced outcomes. For instance, uncontrolled inpatient hyperglycemia, with or without known diabetes, is an independent predictor of worse outcomes [18–20]. Data on baseline and inpatient control of comorbid conditions was not collected in our study. Future analyses of the association of outcomes with comorbid conditions should be stratified according to comorbid control to better describe the possible relationship. In our study, in-hospital mortality was 13.88%, and the mean length of hospitalization was 7.37 days. In-hospital mortality has been reported to be 28% from tertiary care centers in China [21], 21.7% from centers in New York [13], 20% from Iran [22], and 35% in-hospital mortality from a single center study in Italy [23]. Our ICU mortality was 58.8% which is comparable to the estimated case fatality rate ranging from 40% to 59% of ICU admissions who require invasive mechanical ventilation [24–26]. However, there has been wide variability in data reported from different parts of the world. ICU mortality was reported as 26 % from large multicenter case series from Lombardy, Italy [27], 35.8%% from a National cohort study from the UK [28], 31% in a multicenter study from Spain [29], 53% from a large center in New York, USA [30], and 56% from a tertiary care center in India [31]. The heterogeneity in these figures is explained by limited ICU resources particularly in pandemic epicenters and may have been influenced by the age of the affected population [24]. Our ICU mortality rate parallels that which is reported from large centers in both US and India. To better characterize differences in mortality, we determined the risk factors for death among hospitalized patients. Our study showed that multi-organ dysfunction, septic shock, and admission to the intensive care unit on presentation were associated with mortality. These are similar to risk factors reported from other regions across the globe, though individual risk factors have varied [13,32]. Similarly, acute kidney injury was also an independent predictor of mortality as has been reported from various countries as well [32]. Second, on multivariate analysis of laboratory parameters at presentation, only the NLR was found to have a statistically significant association with both disease severity and mortality. CRP, LDH, and creatinine were found to be associated with disease severity alone, whereas ferritin was associated with mortality alone. Associations between higher levels of biochemical and hematological markers of inflammation and organ dysfunction with increasing disease severity and mortality was also observed, consistent with literature from other centers [33]. However, our study supports the early use of NLR as a single marker for risk stratification for both disease progression and mortality, making this cost-effective and readily available tool especially valuable in resource-limited settings. Similar to other studies [34–37], we also found age to be a risk factor for severe disease. A possible explanation for this may be the impaired immune responses with advancing age as both innate and cell-mediated immune mechanisms decline to cause unchecked viral replication and exaggerated proinflammatory cytokine production [38,39]. On the other hand, we did not find an association with the male sex and poor outcomes, and neither did we find the age and sex interaction term to be significant. To understand this further, we evaluated mortality: sex ratios across all age groups; 7.6 for the age interval 50-70 years compared with 2.3 for the age interval of 71-90 years. This highlights the need for disaggregated data to better understand the interaction between biological sex and age and its association with mortality

[40]. We found a greater incidence of nosocomial infections compared to other studies [41–43]. Nosocomial infections were also associated with mortality in univariable analysis, which may be related to immunosuppression with tocilizumab and steroids. This may be an important observation in the context of low-middle income countries where the incidence of nosocomial infections is higher and can contribute to poor outcomes [44] in COVID-19. Our study highlights important differences in factors associated with severity and mortality particularly relevant to a low-middle income country whereby despite a high prevalence of diabetes and increased incidence of nosocomial infections there was comparatively lower in-hospital mortality. One of the reasons for this could be that 66% of the patients were less than 60 years of age and therefore as opposed to developed countries, a relatively younger age group was affected. This may also explain the case fatality rate from Pakistan which has remained around 2-3 % which is considerably lower than Italy and Iran but similar to CFR reported from China and India [45] There has been considerable speculation on the reasons behind this phenomenon and it has been postulated that both genetic and environmental factors may have a role despite the resource constraints [10]. However, some limitations need to be recognized that may limit generalizability. These include retrospective data collection, single-center nature of the study. Moreover, the varying treatment protocols, as more data became available, influenced clinical practices, and may have had bearing on the results of the study.. Notwithstanding limitations, the present study emphasizes the key epidemiological differences in the nature of the outbreak experienced in Pakistan which need to be explored and validated in other similarly situated LMICs and population studies.

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