RESEARCH ARTICLE

Clinical outcomes and predictors of mortality in COVID-19 patients admitted to a High Dependency Unit in Pakistan-a cross-sectional study

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Abstract

Objective: To determine the outcomes and predictors of in-hospital mortality of patients admitted to high-dependency unit with coronavirus disease 2019 infection.

Method: The retrospective study was conducted at a tertiary care hospital in Karachi, and comprised data of adult coronavirus disease 2019 patients of either gender admitted to the high dependency unit from March 1 to June 30, 2020. Outcomes were categorised as patients 'recovered without deterioration', 'deteriorated but survived', and 'deteriorated but expired'. Data was analysed using SPSS 22.

Results: Of the 525 patients with confirmed infection, 245(46.6%) were admitted to the high dependency unit. Leaving out 38(15.5%) cases with missing data, 207(84.5%) cases formed the study sample; 156(75.4%) males and 51(24.6%) females. The overall mean age was 56.9±14years (range: 24-86 years). The most common comorbid condition was hypertension 105(50.7%), and the most common reason for critical care was hypoxic respiratory failure 199(96.1%). Of the total, 153(74%) patients recovered, 31(15%) deteriorated, and mortality was the outcome in 23(11%). There was no significant effect of drug treatment on mortality ($p>0.05$). Age, multimorbidity and high D-Dimer level were significantly associated with disease progression and mortality ($p<0.05$).

Conclusion: Mortality was high among coronavirus disease 2019 patients who were older and had multimorbidity.

Key Words: COVID-19, In-hospital mortality, Multimorbidity, SARS-CoV-2 infection, Critical care outcomes.

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Introduction

By the end of 2022, Severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) resulted in more than 659 million cases of coronavirus disease-2019 (COVID-19) infection, with over 6.6 million deaths worldwide[1]. A tremendous amount of work has been done to identify the mode of disease spread, measures to prevent spread, varied clinical presentation, treatment options, drug efficacy, and the natural course of disease, including morbidity and mortality[2]. Hypoxic respiratory failure has been reported in approximately 15% of COVID-19 cases[3], requiring some forms of ventilatory support, like high-flow nasal cannula, non-invasive (NIV), or invasive mechanical ventilation (MV)[4-6] and escalation of care with transfer to high dependency unit (HDU) or intensive care unit (ICU). The overall mortality in patients admitted to critical care areas ranged between 25.7% and 37.7%[7]. The significant risk factors attributing to high mortality included age >65 years, multiple comorbidities, acute respiratory distress syndrome (ARDS), quick sequential organ failure assessment (qSOFA) score, and increased D-Dimer[8]. Moreover, ethnicity and race are risk factors that may affect an individual's response to the virus and disease outcomes[9].

Located in South Asia, Pakistan had multiple COVID-19 pandemic waves, and by January 2023, there were 1,575,888 cases of COVID-19 with 30,638 deaths were reported[10]. The HDUs are well-equipped and staffed area that act as an intermediate care facility between ICU and the wards. Early identification of risk factors associated with deterioration of patients can result in earlier interventions and improvement in outcomes and mortality rates. While studies have been reported from addressing outcomes of the patients admitted to ICU[3, 11,12], no data is available from Pakistan on the outcomes of patients admitted exclusively to HDUs. The current study was planned to fill the gap by determining the outcomes and predictors of in-hospital mortality of patients admitted to HDU with COVID-19 infection.

Materials and Methods

The observational, retrospective study was conducted at a tertiary care hospital in Karachi, and comprised data from March 1 to June 30, 2020. The study site was a 740-bed tertiary care hospital which is one of the largest university hospitals in Karachi, and provides a broad range of secondary and tertiary care to a wide variety of cases referred from all over Pakistan. The study was

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conducted after approval form the institutional ethics review committee of Aga Khan University Hospital (AKUH), Karachi.

In March 2020, the hospital executed a COVID-19 preparedness plan, anticipating increased COVID-19 patient turnover. Exclusive units were dedicated for confirmed and suspected COVID-19 patients. These units included ward areas, HDU and ICU. The HDUs were four-bed units for confirmed COVID-19 positive patients with a 4:1 patient-to-nurse ratio, equipped with NIV and continuous vital monitoring. For suspected patients, there were separate wards and one-bed isolation rooms in HDU settings. Due to limited resources, only those who required invasive ventilation were managed in the ICU, and the rest of the critically ill patients were managed in HDUs.

Data included in the current study related to adult COVID-19 patients of either gender admitted to the HDU. The COVID-19 infection was diagnosed based on positive polymerase chain reaction (PCR) testing of nasopharyngeal/oropharyngeal swabs. Data of patients shifted from the wards and ICU to the HDU either as step-up and or step-down process were also included.

Data of all suspected patients with negative PCR result, patients with missing data, patients who left against medical advice (LAMA) and those admitted and discharged from the general wards was excluded.

Demographic and significant clinical characteristics, laboratory results, radiological findings, and treatment were recorded. The ratio of arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2) (PF ratio), sequential organ failure assessment (qSOFA) score[13], national early warning (NEWS) score (13) were noted at baseline.

The severity of the COVID-19 was graded as mild, moderate, severe and critical, according to the Clinical Management Guidelines for COVID-19 infections issued by the government of Pakistan[14]. The mild disease was characterised by fever and respiratory symptoms without haemodynamic compromise, need for oxygen, or chest X-ray (CXR) findings. The moderate disease meant a presence of hypoxia or mild infiltrate on CXR or persistent high-grade fever. The severe disease was labelled when there was dyspnoea with hypoxia and with moderate to severe pneumonia. The critical disease was defined as rapid disease progression requiring MV, septic shock, or organ failure that needed ICU monitoring. A worsening renal function was defined as a rise in serum creatinine of 0.3mg/dl or more compared to the value on admission[15]. Fibrosis was defined as the excess of fibrotic tissue in the lung, appearing as reticular shadowing of lung peripheries on CXR. Deterioration was defined as increased oxygen requirement (increment of 1-2 litre from the baseline oxygen requirement after HDU admission), along with the need for an NIV or invasive ventilator, or unstable vital

The primary outcome was the status of the patient at discharge which was categorised as the patient "recovered without deterioration", "deteriorated but survived", and "deteriorated but expired". The secondary outcomes included length of stay (LOS).

Data was analysed using SPSS 22. Continuous variables with normal distributions were reported as mean ± standard deviation (SD) and as median with interquartile range (IQR), if skewed. Frequencies and percentages were calculated for categorical variables. Continuous variables with normal distribution were analysed using one-way analysis of variance (ANOVA), while those with skewed distribution were analysed using Kruskal Wallis test. Univariable logistic regression analysis was done to determine the factors associated with mortality. $P<0.05$ was considered statistically significant. Using the significant risk factors, multivariable logistic regression analysis was done to determine the adjusted effect on mortality. Results were described in crude/unadjusted odds ratio (OR) for univariate analysis and adjusted OR (aOR) with 95% confidence interval (CI) for multivariable logistic regression.

Results

Of the 525 patients with confirmed infection, 245(46.6%) were admitted to the HDU. Leaving out 38(15.5%) cases with missing data, 207(84.5%) cases formed the study sample. Of them, 175(84.5%) patients were admitted to HDU from emergency, 20(9.7%) from the ICU and 12(5.8%) from the wards. There were 156(75.4%) males and 51(24.6%) females. The overall mean age was 56.9±14years (range: 24-86 years). The most common comorbid condition was hypertension (HTN) 105(50.7%). Besides, 91(44%) patients had >2 comorbid conditions, and moderate disease was diagnosed in 95(45.9%) cases. The most common symptom at presentation was fever 171(82.6%), , and the most common reason for critical care was hypoxic respiratory failure 199(96.1%). Of the total, 153(74%) patients recovered, 31(15%) deteriorated, and mortality was the outcome in 23(11%) (Table 1).

On arrival, the median PF ratio and mean NEWS were 263 (IQR: 191-361) and 6.8±3.1, respectively, and 151(72.9%) had a qSOFA score of 1. The air space shadowing and bilateral lung involvement on CXR were seen in

Table-1: Baseline and clinical characteristics.

Variable	Total n=207	Patient Recovered without n=153	Deteriorated but survived n=31	Deteriorated and expired n=23	*p-value*
Age, years	56.9 ± 14.0	55.2 ± 13.0	55.1 ± 14.5	70.3 ± 13.6	<0.001
Gender					
Male	156(75.4)	117(76.5)	23(74.2)	16(69.6)	0.76
Female	51(24.6)	36(23.5)	8(25.8)	7(30.4)	
Two or more comorbids	91(44)	61(39.9)	11(35.5)	19(82.6)	<0.001
Comorbid					
Hypertension	105(50.7)	76(49.7)	15(48.4)	14(60.9)	0.58
Diabetes mellitus	101(48.8)	76(49.7)	12(38.7)	13(56.5)	0.39
Coronary artery disease	36(17.4)	24(15.7)	24(15.7)	10(43.5)	0.001
Chronic kidney disease	19(9.2)	15(9.8)	1(3.2)	3(13)	0.40
Mode of Admission					
Emergency	198(95.7)	148(96.7)	29(93.5)	21(91.3)	0.40
Elective	9(4.3)	5(3.3)	2(6.5)	2(8.7)	
Severity of disease					
Mild	23(11.1)	16(10.5)	4(12.9)	3(13)	0.07
Moderate	95(45.9)	75(49)	15(48.4)	5(21.7)	
Severe	85(41.1)	60(39.2)	12(38.7)	13(56.5)	
Critical	4(1.9)	2(1.3)	0	2(8.7)	
Reason for admission to HDU					
Hypoxic respiratory failure	199(96.1)	148(96.7)	28(90.3)	23(100)	0.14
Need of NIV	120(58)	76(49.7)	25(80.6)	19(82.6)	<0.001
Acute kidney injury	47(22.7)	31(20.3)	5(16.1)	11(47.8)	0.008
Worsening hypoxia	16(7.7)	4(2.6)	6(19.4)	6(26.1)	<0.001
Bacterial pneumonia	10(4.8)	7(4.6)	1(3.2)	2(8.7)	0.62
Septic/ Cardiogenic Shock	7(3.4)	3(2.0)	0	4(17.4)	<0.001
Fungal pneumonia	5(2.4)	1(0.7)	2(6.5)	2(8.7)	0.01
Vitals					
Oxygen Saturation	87.9 ± 10.7	87.9 ± 10.3	90.2 ± 8.9	84.7 ± 14.9	0.18
Respiratory rate	28.0 ± 7.6	28.0 ± 7.4	26.9 ± 7.2	29.0 ± 9.0	0.61
Temperature	37.1 ± 0.9	37.1 ± 1.0	37.1 ± 0.7	36.8 ± 0.4	0.4
Heart rate	91.9 ± 15.6	97.5 ± 17.5	98.6 ± 24.5	91.9 ± 3.2	0.35

HDU: High dependency unit, NIV: Non-invasive mechanical ventilation.

198(95.7%) and 189(91.3%) patients, respectively. Further, 170(82.1%) patients received steroids and 72(34.8%) received tocilizumab. Median length of HDU stay was 5 days (IQR: 2-8 days). Upon discharge, 177(85.5%) and 178(86%) patients had positive COVID-19 PCR and mild disease, respectively (Table 2).

Among those who expired, higher age, ≥2 comorbidities, ischaemic heart disease (IHD) and septic/cardiogenic shock were significant factors (p<0.05). Also, the non-survivors had a low PF ratio (PA02/Fi02), decreased platelet count, raised creatinine, Gamma-glutamyl transferase (GGT), procalcitonin (PCT), troponin I (Trop I), pro-brain natriuretic peptide (PBNP) and D-Dimer levels, as well as cavitary lesion on CXR (p<0.05). There was no significant relationship of NEWS and qSOFA with mortality (p>0.05).

Table-2: Laboratory parameters at the time of HDU admission and management.

	Total n=207	Recovery without deterioration n=153	Deteriorated but survived n=31	Deteriorated and expired n=23	p-value
PF ratio*(PA02/Fi02)	263(191-361)	261(198.5-340)	342(242-396)	214(105-323)	.01$
NEWS score	6.8 ± 3.1	6.8 ± 3.2	6.6 ± 3.0	7.3 ± 2.9	0.65
qSOFA score- 0	44(21.3)	33(21.6)	6(19.4)	5(21.7)	
1	151(72.9)	112(73.2)	24(77.4)	15(65.2)	0.58
2	12(5.8)	8(5.2)	1(3.2)	3(13)	
TLC *(x10^9/L)	8.2(6.0-11.9)	8.2(6.4-12.0)	8.1(5.3-10.1)	8.6(5.9-12.5)	0.46$
NLR ratio*	6.0(3.0-10)	6.0(3.0-9.2)	6.0(2.7-10.2)	9.3(4-13)	0.20$
Haemoglobin(g/dl)	12.6 ± 2.4	12.5 ± 2.0	13.5 ± 4.0	12.4 ± 2.3	0.1
Platelets*(x10^9/L)	231.5(178-311.2)	245(187-328.5)	193(148-255)	190(130-265)	0.002$
Creatinine*(mg/dL)	1.1(0.9-1.6)	1.1(0.9-1.5)	1.0(0.8-1.4)	1.5(1.0-2.5)	0.03$
Albumin; n=47	3.4 ± 0.7	3.3 ± 0.7	3.6 ± 0.3	3.2 ± 0.4	0.63
AST*; n=155	44(32-69)	43(31.5-78)	39.5(31-54.7)	52(35-86)	0.33$
ALT*; n=154	56(38-76.2)	56(38-75)	51(37.5-75.2)	71(40-107)	0.35$
GGT*; n=154	75.5(41.7-141)	79(49-145.5)	41.5(27.7-82.2)	105(24-194)	0.03$

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ALP*; n=153	92(71-137)	92(73-142.5)	88(54.7-121.5)	108(75-125)	0.31$
CRP*(mg/L); n=181	119(56.4-182.1)	125.1(59.6-182.5)	99.1(29.9-188.9)	142.5(62.3-164.9)	0.53$
Procalcitonin(ng/ml);n=186	0.19(0.09-0.5)	0.2(0.1-0.5)	0.08(0.05-0.4)	0.3(0.1-1.7)	0.006$
Ferritin*(ng/ml); n=163	844.5(395-1388)	795(372.4-1378)	828.6(378-1375)	1166(780-2034)	0.15$
LDH*(I.U/L); n=159	475(374-575)	474.5(368.7-560.7)	493(365-566)	574.5(386.7-725.5)	0.37$
Troponin I(ng/mL) *; n=180	0.01(0.006-0.06)	0.01(0.006-0.04)	0.01(0.006-0.04)	0.07(0.02-0.2)	0.002$
PBNP (pg/ml)*; n=72	493.5(190-2148)	379(130.1-1460)	346(172-3802)	6615(904.5-21617)	0.007$
D-Dimer(mg/ml) *; n=147	1.0(0.6-2.7)	1.0(0.6-1.9)	0.8(0.4-1.8)	4.7(0.9-8.8)	0.02$
Treatment					
Hydroxychloroquine	82(39.6)	52(34)	21(67.7)	9(39.1)	0.002
Azithromycin	126(60.9)	89(58.2)	23(74.2)	14(60.9)	0.24
Tocilizumab	72(34.8)	50(32.7)	13(41.9)	9(39.1)	0.55
Convalescent plasma	16(7.7)	8(5.2)	5(16.1)	3(13)	0.07
Methyl Prednisolone	170(82.1)	125(81.7)	24(77.4)	21(91.3)	0.4
Awake proning	18(8.7)	14(9.2)	2(6.5)	2(8.7)	0.88
HDU stay, days*	5(2.0-8.0)	4(2.0-6.0)	9(5.0-11)	8(3-17)	<0.001$
Ward stays, days*	1(0-3)	2(0-3.0)	2(0-8.0)	0(0-0)	<0.001$
Hospital stay, days*	8(5.0-12)	7(5-10)	13(9-19)	16(6-21)	<0.001$
Time to deterioration after admission-					
Within 24 hours	8(3.86)	0	7(22.5)	1(4.3)	
After 24 hours	9(4.34)	0	5(16.1)	4(17.39)	0
After 48 hours	2(0.96)	0	1(3.2)	1(4.3)	
After 72 hours	35(16.9)	0	18(58)	17(73.9)	
PCR positive on discharge	177(85.5)	132(86.3)	26(83.9)	19(82.6)	0.86
Severity of disease on discharge					
Mild	178(86)	149(97.4)	29(93.5)	0	<0.001
Moderate	18(8.7)	4(2.6)	2(6.5)	12(52.2)	
Severe	8(3.9)	0	0	8(34.8)	
Critical	3(1.4)	0	0	3(13)	

*Median (IQR), $Kruskal Wallis test was used for the three-groups

HDU: High dependency unit, qSOFA: Quick sequential organ failure assessment score, NEWS: National early warning score, TLC: Total leukocyte count, NLR ratio: Neutrophil-to-lymphocyte ratio, ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, CRP: C-reactive protein, LDH: Lactate dehydrogenase, PBNP: Pro-brain natriuretic peptide.

There was no significant effect of drug treatment on mortality (p>0.05). Median LOS was 8 days (IQR: 5-12 days), with the longest median stay 16 days (IQRL 6-21 days) being in the group that expired (p<0.05).

Complications observed in HDU patients during hospital stay were hospital-acquired pneumonia (HAP) 19(9.2%), fungal pneumonia 10(4.8%), septic shock 4(1.9%), catheter-associated urinary tract infections (CAUTI) 2(0.9%), and central line-associated bloodstream infections (CLABSIs) 1(0.5%).

Univariate logistic analysis found that age (OR: 1.10; 95% CI: 1.10-1.15; p<0.001), >2 comorbidity (OR: 7.38; 95% CI: 2.41-22.60; p<0.001), need of NIV (OR: 3.10; 95% CI: 1.21-7.91; p<0.01), septic shock (OR: 12.70; 95% CI: 2.64-61.04; p=0.002), low PF ratio (OR: 0.99; 95% CI: 0.99-0.99; p=0.02), high PBNP (OR: 0.04; 95% CI: 1.0-1.0; p=0.04), increased HDU stay (OR: 1.15; 95% CI: 1.07-1.23; p=0.001), and increased hospital stay (OR: 1.09; 95% CI: 1.04-1.15; p= 0.001) were significantly associated with disease progression and mortality.

Table-3: Multivariate analysis for factors predicting mortality.

	aOR (95% CI)	p-value
Age, years	1.09(1.03-1.17)	0.004
Two or more comorbid		
No	1	
Yes	7.21(1.18-43.85)	0.03
D-Dimer(mg/ml)	1.12(1.02-1.23)	0.01
Platelets x10^9/L)	0.99(0.98-1.0)	0.04

aOR: Adjusted Odds Ratio

Multivariate logistic analysis indicated that age (aOR: 1.09; 95% CI: 1.03-1.17; p=0.004), multimorbidity (aOR: 7.21; 95% CI: 1.18-43.85; p=0.03), high D-Dimer (aOR: 1.12; 95% CI: 1.02-1.23, p=0.01), and low platelet count (aOR: 0.99; 95% CI: 0.98-1.0, p=0.04) were risk factors predicting mortality (Table 3).

Discussion

The mortality associated with severe and critical COVID-19 infection is very high[7, 8]. With an increasing number of COVID-19 patients, HDU offers more extensive care than general ward. Patients can be transferred from HDU to ICU if they deteriorate, or from ICU to HDU as a step-down process providing intermediate acuity bed in a poor-resource country like Pakistan.

The patient's characteristics admitted to critical care in the current study were similar to earlier studies[8]. The majority population were males, and the most common symptoms were cough, fever and shortness of breath[8, 12,16]. Similar to a study[17], HTN, diabetes mellitus (DM) and IHD were the most common comorbidities in the current study. Other studies have also reported cerebrovascular disease, IHD, chronic kidney disease (CKD, and chronic obstructive pulmonary disease (COPD) as the most common comorbid conditions[8, 12].

The current cohort indicated deterioration in 26% (n=54) patients and mortality of around 11% (n=23). However, others have reported mortality of 24.5% to 37.7%[3, 18-20]. The mortality reported was higher in other cohorts as intubated patients were also included in the sample population. The mortality associated with COVID-19 infection in the deterioration group was significant, with 1-2 weeks of survival time for non-survivors after admission to the critical care unit, and it was in line with published data[8, 21].

The disease progression and mortality in critical patients with COVID-19 have been reported to be associated with older age (median age≈60 years) and multi-morbidities[3, 8, 16,18, 22]. The current study had similar findings. The most common comorbidity in non-survivors in the present study was IHD and heart failure, which was consistent with the finding of Mandeep et al.[8], who showed that coronary artery disease and heart failure were linked to high mortality. They also reported that conditions like COPD and smoking were linked to an elevated risk of in-hospital mortality, which contradicted the current findings. The earlier as well as the current study related to data about mortality from Asian countries. However, the current data differs from the other study, in which the most prevalent comorbidities among non-survivors were DM and cerebrovascular disease[8].

Comparable to other studies, the disease progression was higher among patients who had high D-Dimer and worsening renal function. It has been reported that patients with D-dimer levels >2.0µg/mL have a higher incidence of mortality compared to those with <2.0µg/mL[22,23]. In addition, a decrease in creatinine clearance also increases the probability of death, and the trend persists even after excluding chronic renal failure from the analysis[24].

It was observed in the current study that patients with thrombocytopenia, increased PBNP and PCT were more likely to deteriorate in hospital and to have a fatal outcome. This was in line with literature[25-27]. Liu et al. reported increased C-reactive protein (CRP) and decreased albumin on admission as an important indicator for disease progression[17,18], which was not found in the current study.

The incidence of complications observed in HDU patients during hospital stay in a tertiary care hospital in Spain was HAP(23%), fungal pneumonia (15%), septic shock (60%), CAUTI (8%), and CLABSIs (25%)[19]. Similar complications were observed in the current study, but were less frequent, which could be due to early identification of patients at risk for deterioration and timely provision of care.

Bacterial and fungal co-infection was a common complication in critically ill patients in a study[19] which is consistent with the current observations.

The current study has some limitations. First, it is a single-centre retrospective study with a small sample size which may affect generalisability. Secondly, it only studied COVID-19 patients admitted to HDU, excluding those requiring invasive ventilation and do-not-resuscitate (DNR) patients; hence mortality rate and risk factors elucidated will apply only to patients with moderate to severe disease. Out of 245 patients, data of 37 patients was excluded due to missing elements, which might have affected the outcome. The actual mortality rate may have been underestimated as the study only reported in-hospital mortality and the patients were not followed up post-discharge.

Conclusion

The mortality of patients with COVID-19 infection admitted to HDU was higher in older patients and those with multimorbidity. Physicians should closely monitor patients with older age, IHD, and impaired renal function on admission. The mortality rate in the at-risk group can be reduced by focussing on the risk factors leading to deterioration.

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