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Coronavirus Pandemic

Predictors of mortality among hospitalized hypertensive patients with COVID-19 during third and fourth waves in Pakistan

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Abstract

Introduction: Hypertension significantly contributes to the severity and mortality of COVID-19 patients. It has also been a risk factor for prolonged hospitalization and the need for intensive care. However, the data is still evolving. Therefore, this study investigated the predictors of mortality among hypertensive COVID-19 patients.

Methodology: A single-center cohort study was performed at Indus Hospital and Health Network, Karachi, Pakistan, between April 1, 2021, and October 31, 2021. This study included 333 hospitalized hypertensive COVID-19 patients and evaluated their clinical characteristics and survival outcomes. A multivariate logistic regression model was applied in IBM SPSS 27.0 to determine the predictors of mortality.

Results: The majority of patients were females (54.7%), the median age was 62 [55-70] years, with co-existing diabetes (56.5%) and severely ill (52.6%). The independent predictors of mortality identified were age ≥ 65 years (aOR 20.89, 95% CI, 5.81-75.15; $p < 0.001$), pulse rate (aOR 1.03, 95% CI 1.01-1.63; $p = 0.006$), serum creatinine (aOR 1.34, 95% CI 1.11-1.63; $p = 0.002$), use of antibiotics (aOR 3.40, 95% CI 1.29-8.98; $p = 0.014$)), corticosteroid (aOR 49.68, 95% CI 1.83-1350.31; $p = 0.020$), and who needed high flow oxygen supply (aOR 13.08, 95% CI 1.70-100.54; $p < 0.001$), non-invasive mechanical ventilation (aOR 229.01, 95% CI 29.30-1789.71; $p < 0.001$) and invasive mechanical ventilation (aOR 379.54, 95% CI 36.60-3935.87; $p < 0.001$).

Conclusions: Our study suggests that older age, elevated pulse rate, serum creatinine, use of antibiotics and corticosteroids, and the need for mechanical ventilation predict mortality among hypertensive COVID-19.

Key words: COVID-19; hypertension; intensive care; mortality; Pakistan; severity.

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Introduction

Soon after the outburst of Coronavirus disease 2019 (COVID-19), which started in China in December 2019 [1], the swift escalation in infection counts throughout the world made it a pandemic on March 12, 2020, as proclaimed by the World Health Organization (WHO) [2]. So far, the pandemic has affected over 213 countries worldwide, including Pakistan. As of July 5, 2023, WHO has recorded more than 767 million COVID-19 cases and more than 6.9 million deaths globally [3]. Moreover, Pakistan has recorded over 1.58 million cases of COVID-19, with over 30,000 deaths across the country [4].

Pakistan observed the first and second waves of COVID-19 from March to July 2020 and October 2020 to January 2021, respectively. Despite the vaccination drives against COVID-19 in February 2021, the third wave of COVID-19 was observed as the positivity rate again surpassed >10% of all tests performed in the country in March 2021 [5]. The cases peaked by April of the same year and later declined gradually. Following a declining trend of cases, in July 2021, there was a resurge of cases of COVID-19 which witnessed a

fourth wave in Pakistan [6]. On April 17, 2021, the maximum number (6127) of positive cases was seen in the public and private sector healthcare facilities during the third and fourth waves. Moreover, despite the initiation of vaccination drives against COVID-19 in the country, the population's hesitancy towards COVID-19 vaccination [7] led to a lower immunization rate. In addition, these waves of the COVID-19 pandemic were driven by more transmissible variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for excessive hospitalization and higher mortality rates than the variants during the previous waves in the country [7,8].

According to the WHO, cardiovascular diseases are responsible for 29% of deaths in the Pakistani population [9]. Furthermore, studies have revealed that COVID-19 patients with comorbid illnesses can have poor clinical outcomes [10-12]. Moreover, it has also been found that hypertension (HTN) is a risk factor among severely infected COVID-19 patients [12]. In addition, some laboratory indicators, such as lower lymphocyte count and higher D-dimer levels are also linked with mortality [13,14]. In previous studies, the prevalence of HTN in COVID-19 patients [10,14] ranged from 15% to 30%, which is even higher in non-survivors [15,16]. Since HTN is a common health issue in adults, especially in elderly populations, therefore, it has been reported as a commonly existing comorbidity in COVID-19 patients [10,14,17] and is considered a predisposing factor for a prolonged hospital stay, intensive care, and death among infected patients [18,19]. In addition, complications and mortality of COVID-19 are also higher among older people [11]. Moreover, renin-angiotensin-aldosterone system (RAAS) inhibitors, angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme inhibitors (ACEIs) may enhance the production of angiotensin-converting enzyme 2 (ACE2), which is required for entrance and propagation of SARS-CoV-2, the coronavirus strain that causes COVID-19 [20,21]. Thus, COVID-19 patients receiving RAAS inhibitors should be at higher risk of worse outcomes [22,23], by acting on renin angiotensin aldosterone system by two different mechanisms [24]. This has led to speculation that these drugs may increase susceptibility to COVID-19 due to increased expression of ACE2 or worsen its outcomes by promoting lung injury. On the contrary, experimental studies have shown that ACE2 protects against lung injury [25,26]. However, the data is lacking on the impact of demographic and clinical characteristics on the outcomes of hospitalized hypertensive patients with COVID-19 in Pakistan during the third and fourth waves. Therefore, the current study specifically aims to determine the predictors of mortality by comparing the general characteristics, clinical presentation, treatment, and complications between dead and recovered COVID-19 patients with hypertension.

Methodology

Study design and sampling

We performed a single-center, observational, prospective cohort study at Indus Hospital and Health Network (IHHN), Korangi campus (a tertiary care hospital) in Karachi, Pakistan. IHHN Korangi campus is a multidisciplinary tertiary care hospital with a capacity of 300 beds, providing round-the-clock health facilities through inpatient and emergency departments and serving more than 2,500 patients at outpatient clinics daily. Since the beginning of the COVID-19 pandemic, IHHN has dedicated a 26-beds ward for COVID-19-infected patients. In addition, a separate section was established in emergency for suspected COVID-19 patients to avoid mixing suspected and confirmed COVID-19 cases. Later, the number of beds was enhanced to 45, designated for COVID-19.

Using a non-probability purposive sampling method, we enrolled all the COVID-19 patients with hypertension who were admitted to the high dependency unit (HDU) and intensive care unit (ICU) designated for COVID-19, from April 1, 2021, till October 31, 2021, during the third and fourth waves of COVID-19 in Pakistan. The attending physician took patients' demographic information, clinical characteristics, and past medical history. The information on hypertension and other comorbidities, such as diabetes mellitus, was confirmed by a written physician's note for diagnosis and existing comorbidities in the medical record. The physicians established at the time of admission that patients were hypertensive according to the International Society of Hypertension Global Hypertension Practice Guidelines [27]. These patients had pre-existing hypertension for longer periods. Patients' inclusion criteria were: adults (aged ≥ 18 years), having a positive test for SARS-CoV-2 through real-time reverse transcriptase-polymerase chain reaction (RT-PCR), with a history of known hypertension (HTN) with or without other concurrent comorbidities such as diabetes mellitus, admitted to COVID-19 wards of the hospital for at least 24 hours, with the definite outcome (death or recovery). We excluded the patients: with incomplete clinical information, without definite outcomes (recovered or dead), pregnant women and children under 18 years,

and COVID-19 patients without hypertension, as shown in Figure 1.

Data collection tool and procedure

A team of researchers, a pharmacist, and a consultant cardiologist extracted the data from the patient's electronic medical record. The researcher and pharmacist reviewed the collected data independently, while the cardiologist was consulted for any disagreement. The data were recorded on a pre-designed data collection form. Variables of the study included patients' demographic characteristics (age, gender, comorbidities, COVID-19 vaccination status), duration of illness (time between the first sign or symptom and date of admission), clinical presentations, baseline vital signs and laboratory findings, the severity of cases, and treatments. The study outcome was health status (death or recovery) till November 15, 2021. Patients were followed during hospitalization till they either recovered or died. All the patients were categorized as mild, moderate, severe, and critical based on the COVID-19 guidelines recommended by the National Institute of Health, Rockville Pike, Bethesda, Maryland [1].

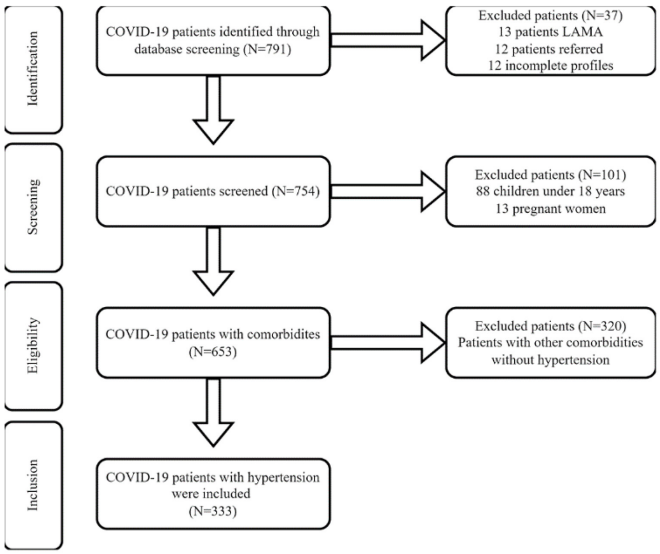
Laboratory reference ranges

The reference ranges for various laboratory reports were; serum calcium (Sr. Ca) 8.4-10.2 mg/dL, hemoglobin (Hb) 11.1-16.3 g/dL, total leukocytes count (TLC) 4-10 × 10^9/L, neutrophils 40-70%, lymphocytes 20-45%, platelets 150-400 × 10^9/L, serum creatinine (Sr. Cr) 0.57-1.25 mg/dL, high sensitivity Troponin I (Trop I) up to 34.2 ng/L, serum sodium (Na) 136-145 mEq/L, serum chloride (Cl) 98-107 mEq/L, serum potassium (K) 3.5–5.1 mEq/L, serum bicarbonate (HCO3) 22-29 mEq/L.

The reference ranges for liver function tests (LFTs) were gamma-glutamyl transferase (GGT) < 55 U/L, alanine transaminase (ALT) < 45 U/L, and alkaline phosphate 40-150 U/L. The normal range for prothrombin time was (PT) 11-16 sec.

Inflammatory marker reference ranges were; C-reactive proteins (CRP) < 0.5 mg/L, D-dimers up to 0.5 ug/mL, serum ferritin 20-250 ng/mL, lactate dehydrogenase (LDH) 125-220 U/L, procalcitonin (ProCal) < 0.046 ng/mL [28].

Figure 1. Patients' inclusion and exclusion criteria.



Statistical analysis

Data analysis was done using SPSS v.27 from IBM Corporation, Armonk, NY. Continuous variables were expressed in median and interquartile range (IQR), as they were non-normally distributed (Kolmogorov-Smirnov tests, all $p < 0.05$), and categorical variables in frequencies and percentages. Mann-Whitney U test, Chi-squared test, or Fisher's Exact test was applied to compare the variables between dead and recovered groups, as appropriate. Since the outcome variable was dichotomous, i.e., Death or Recovery, we applied a binary logistic regression. In addition, univariate and multivariate regression was applied to investigate the predictors of mortality. A cut-off p value ≤ 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

Seven hundred ninety-one confirmed COVID-19 patients were admitted to the COVID-19 ward from April 1, 2021, to October 31, 2021. Of them, 333 (42.09%) patients had hypertension (HTN) and were involved in the study. Out of 333 patients, the majority were females (54.7%), with a median age of 62 (55-70) years and age < 65 years (55.9%), and 8.1% were fully vaccinated against COVID-19. Diabetes mellitus (DM) (56.5%) was the frequently observed comorbidity among hypertensive COVID-19 patients, followed by other cardiovascular diseases (27.9%) and chronic kidney disease (10.8%). More than half (52.6%) of the patients presented with severe illness; the median duration was 7 (4-11) days. Furthermore, the patients appeared with symptoms including shortness of breath (83.8%), self-reported fever (83.8%), productive cough (38.7%), and generalized weakness (28.5%). Regarding baseline vital signs, the median of systolic blood pressure (SBP) was 140 (123-156) mmHg, diastolic blood pressure (DBP) 80 (70-89) mmHg, pulse rate

(PR) 95 (81-110) beats per minute, the temperature 36.8 C (36.8-37.1), respiratory rate (RR) 30 (24-36) breaths per minute, and oxygen saturation (sPO_2) 85% (76-90). 147 (44.1%) died, and 186 (55.9%) recovered until November 15, 2021, as shown in Table 1.

Table 1 also compares patients' characteristics based on their health status (death or recovery). There was no significant difference in mortality while comparing gender, presence of concomitant comorbidities, and median duration of illness (all $p > 0.05$). However, mortality was significantly associated with the median age in years ($p < 0.046$), age groups ($p = 0.043$), and baseline severity level ($p < 0.001$), as shown in Table 1.

Patients' clinical presentation and baseline vital signs at admission are also shown in Table 1. Only shortness of breath (89.8% vs 75.8%, $p < 0.001$) was associated with mortality during the investigation.

There was a significant association between the median (IQR) pulse rate [101 (86-116) vs 90 (79-102), $p < 0.001$], respiratory rate [32 (28-38) vs 28 (22-32), $p < 0.001$] and median oxygen saturation at the time of

Table 1. General characteristics and clinical presentation of hypertensive COVID-19 patients.

Variables	Frequency (%) or Median (IQR)	Dead (N = 147)	Recovered (N = 186)	*p-value*
Gender				
Female	182 (54.7)	85 (57.8)	97 (52.2)	0.302[α]
Male	151 (45.3)	62 (42.2)	89 (47.8)	
Age in years	62 (55-70)	65 (57-72)	61 (53-68)	**0.046**[b]
Age Groups				
< 65 years	186 (55.9)	73 (49.6)	113 (60.7)	**0.043**[α]
≥ 65 years	147 (44.1)	74 (50.4)	73 (39.3)	
Comorbidities				
Diabetes	188 (56.5)	84 (57.1)	104 (55.9)	0.822[a]
Cardiovascular disease	93 (27.9)	40 (27.21)	53 (28.5)	0.795[a]
Chronic kidney disease	36 (10.8)	15 (10.2)	21 (11.3)	0.751[a]
Cerebral vascular arrest	17 (5.1)	6 (4.0)	11 (5.9)	0.874[a]
Asthma	13 (3.9)	6 (4.0)	7 (3.7)	0.882[a]
BPH	10 (3.0)	6 (4.0)	4 (2.1)	0.240[c]
Hepatitis	10 (3.0)	3 (2.0)	7 (3.7)	0.281[c]
Hypothyroidism	9 (2.7)	4 (2.7)	5 (2.7)	0.621[c]
COPD	6 (1.8)	5 (3.4)	1 (0.5)	0.062[c]
Other*	20 (6.0)	13 (8.8)	7 (3.7)	0.053[a]
COVID-19 vaccination				
Non-vaccinated	291 (87.4)	129 (87.7)	162 (87.1)	
Partially vaccinated	15 (4.5)	5 (3.4)	10 (5.4)	0.641
Fully vaccinated	27 (8.1)	13 (8.8)	14 (7.5)	
Baseline Severity				
Mild	30 (9.0)	3 (2.1)	27 (14.5)	
Moderate	37 (11.1)	3 (2.1)	34 (18.3)	**< 0.001**[a]
Severe	175 (52.6)	73 (49.6)	102 (54.8)	
Critical	91 (27.3)	68 (46.2)	23 (12.4)	
Signs and symptoms				
Fever	279 (83.8)	129 (87.7)	150 (80.6)	**0.080** [a]
Shortness of breath	273 (82.0)	132 (89.8)	141 (75.8)	**< 0.001**
Productive cough	129 (38.7)	62 (42.2)	67 (36.1)	0.252
Weakness	95 (28.5)	48 (32.6)	47 (25.3)	0.138
Dry cough	56 (16.8)	27 (18.4)	29 (15.6)	0.501
Vomiting	40 (12.0)	13 (8.8)	27 (14.5)	0.114
Malaise	36 (10.8)	19 (12.9)	17 (9.1)	0.269
Chest pain	32 (9.6)	11 (7.5)	21 (11.3)	0.242
Diarrhea	29 (8.7)	9 (6.1)	20 (10.7)	0.137
Chills and rigors	23 (6.9)	12 (8.1)	11 (5.9)	0.422
Abdominal pain	17 (5.1)	9 (6.1)	8 (4.3)	0.453
Anorexia	29 (8.7)	15 (10.2)	14 (7.5)	0.390
Sore Throat	14 (4.2)	8 (5.4)	6 (3.2)	0.317
Others**	60 (18.0)	32 (21.8)	28(15.1)	0.113
Vital signs, Median (IQR)				
Systolic Blood Pressure	140 (123-156)	140 (128-158)	139 (120-154)	0.072[b]
Diastolic Blood Pressure	80 (70-89)	80 (70-89)	80 (70-89)	0.853
Pulse Rate	95 (81-110)	101 (86-116)	90 (79-102)	**< 0.001**
Temperature (ºC)	36.9 (36.9-37.1)	36.9 (37.1-37.2)	36.9 (36.9-37)	0.221
Respiratory Rate	30 (24-36)	32 (28-38)	28 (22-32)	**< 0.001**
O_2 saturation	85 (76-90)	80 (70-85)	89 (84-93)	**< 0.001**
Duration of illness in days	7 (4-11)	7 (5-11)	7 (4-11)	0.384[b]

*Epilepsy, Parkinson's disease, Arthritis, Gout, Chronic liver disease, Systemic lupus erythematosus, **Tiredness, anorexia, constipation, confusion, altered consciousness, insomnia, poly-uria, fits, and palpitation; a Pearson Chi-squared; b Mann Whitney U test; c Fisher's Exact test.

admission [80 (70-85) vs 89 (84-93), $p < 0.001$] with mortality (Table 1).

Laboratory findings

The baseline laboratory results were compared between deceased and recovered patients and were presented as Median (IQR) in Table 2. There was no significant association between serum hemoglobin, platelets, potassium, and chloride levels with mortality (all $p > 0.05$). On the other hand, there was a significant difference in total leukocyte count ($p < 0.001$), neutrophils ($p < 0.001$), lymphocytes ($p < 0.001$), monocytes ($p < 0.001$), high sensitivity troponin I ($p < 0.001$), serum creatinine ($p = 0.003$), and serum bicarbonate ($p = 0.003$), and gamma-glutamyl transferase ($p = 0.003$) between dead and recovered patients. Additionally, the inflammatory markers, including C-reactive protein ($p < 0.001$), D-dimers ($p = 0.001$), serum ferritin ($p < 0.001$), lactate dehydrogenase ($p < 0.001$), and pro-calcitonin ($p < 0.001$) were significantly higher in dead patients compared to recover, as shown in Table 2.

Treatment and complication of hypertensive COVID-19 patients

Past antihypertensive therapy (Supplementary Table 1), treatment during hospital stay, and complications of hypertensive COVID-19 patients are summarized in Table 3. Most patients were prescribed antiviral (76.3%), antibiotics (55.3%), and antifungals (8.7%), corticosteroids (87.4). More than 4/5 of the patients, 270 (81.1%), received different antihypertensive therapies. Of them, 19.3% were administered with ACEI/ARBs and 96.7% with Non-ACEI/ARBs antihypertensives. Based on the need for respiratory support, 38.4% need non-invasive mechanical ventilation.

Table 3 also elucidates the association of mortality with treatments and complications of patients. It was observed that there was a strong association between the use of antibiotics ($p < 0.001$), antifungal drugs ($p < 0.001$), systemic corticosteroids ($p < 0.001$), ACEI/ARB therapy ($p < 0.001$), and type of respiratory support ($p < 0.001$) with mortality.

While comparing patients' complications, there was also a significant association of cardiac arrest ($p < 0.001$), sepsis ($p < 0.001$), acute respiratory distress syndrome (ARDS) ($p = 0.001$), and multiple organ

Table 2. Baseline laboratory findings among hypertensive COVID-19 patients.

Laboratory findings, Median (IQR)	Dead (N = 147)	Median (IQR)	Recovered (N = 186)	Median (IQR)	*p-value* [a]
Blood Cells Count					
Hb	147	12.3 (10.5-13.7)	186	12.3 (10.3-13.3)	0.272
TLC	147	13.0 (8.3-18.3)	186	9.9 (6.9-13.7)	**< 0.001**
Neutrophils	147	86.4 (81.7-92.8)	186	82.5 (74.7-88.1)	**< 0.001**
Lymphocyte	147	7.1 (3.6-12.3)	186	10.2 (5.9-16.2)	**< 0.001**
Monocytes	147	4.1 (2.6-6.5)	186	5.4 (3.5-7.8)	**< 0.001**
Eosinophils	147	0.0 (0.0-0.2)	186	0.1 (0.0-0.5)	**0.020**
Basophils	147	0.3 (0.2-0.7)	186	0.4 (0.2-0.7)	0.294
PLTs	147	236 (180-335)	186	233 (185-320)	0.732
Biomarker					
HS Tropi I	142	53 (13-293)	175	13 (4-60)	**< 0.001**
Serum Creatinine and Electrolytes					
Sr. Cr	147	1.2 (0.8-2.3)	186	1.0 (0.7-1.5)	**0.003**
Na	147	138 (132-141)	186	135 (133-139)	**0.009**
K	147	4.1 (3.8-4.7)	186	4.1 (3.7-4.5)	0.298
Cl	147	103 (97-107)	186	101 (98-105)	0.272
HCO_3	147	19.1 (15.9-22.4)	186	21.1 (18.3-24.3)	**0.002**
Liver Function Test and blood clotting indicator					
GGT	140	70 (42-149)	172	55 (31-100)	**0.002**
ALT	140	32 (22-58)	172	31 (18-48)	0.091
Alkaline phosphate	140	97 (75-158)	172	94 (72-122)	0.096
PT	140	11.1 (10.4-12.2)	172	10.9 (10.5-11.8)	0.658
INR	140	1.0 (0.9-1.2)	172	1.0 (1.0-1.1)	0.624
Inflammatory markers					
CRP	147	150.0 (76.9-215.5)	183	99.8 (44.4-163.5)	**< 0.001**
D-Dimer	123	1.6 (0.9-2.8)	160	0.9 (0.4-2.3)	**< 0.001**
Sr. Ferritin	142	915.4 (442.9-1675.5)	178	602.7 (258.0-1343.1)	**< 0.001**
LDH	147	624 (462-808)	186	407 (297-550)	**< 0.001**
Procalcitonin	143	0.5 (0.2-1.3)	181	0.2 (0.1-0.5)	**< 0.001**

IQR: Interquartile range; Sr.Ca: Serum calcium; Hb: Hemoglobin; TLC: Total leucocytes count; PLTs: Platelets; HS Tropi I: High sensitivity Troponin I; Sr. Cr: Serum creatinine; Na: Sodium; K: Potassium; Cl: Chloride; HCO_3: Bicarbonate; GGT: Gamma-glutamyl transferase ; ALT: Alanine transaminase; PT: Prothrombin time; INR: International normalize ratio; CRP: C-reactive proteins; and LDH: Lactate dehydrogenase. a Mann-Whitney U test.

Table 3. Treatment and complications among hypertensive COVID-19 patients.

Variables	N (%)	Dead (N = 147)	Recovered (N = 186)	*p* value [a]
Treatment				
Antiviral therapy	254 (76.3)	117 (79.6)	137 (73.6)	0.206
Antibiotic therapy	184 (55.3)	106 (72.1)	78 (41.9)	**< 0.001**
Antifungal therapy	29 (8.7)	24 (16.3)	5 (2.7)	**< 0.001**
Corticosteroids	291 (87.4)	140 (95.2)	151 (81.2)	**< 0.001**
Anticoagulants	222 (66.7)	103 (70.1)	119 (64.0)	0.242
Insulins	194 (58.3)	83 (56.6)	111 (59.6)	0.316
Oral hypoglycemic agents	11 (3.3)	2 (1.4)	9 (4.8)	0.069
Antihypertensive therapy				
ACEI/ARB therapy	52 (19.3)	12 (8.2)	40 (21.5)	**< 0.001**
Non- ACEI/ARB therapy	261 (96.7)	111 (75.5)	126 (67.7)	0.179
Respiratory support				
O_2 supply through NP or FM	80 (24.0)	7 (4.7)	73 (39.2)	**< 0.001**
O_2 supply through HNFC	42 (12.6)	10 (6.8)	32 (17.2)	**0.005**
NMV	128 (38.4)	96 (65.3)	32 (17.2)	**< 0.001**
IMV	40 (12.0)	31 (21.1)	9 (4.8)	**< 0.001**
Complications				
Cardiac Arrest	98 (29.4)	96 (65.3)	2 (1.1)	**< 0.001**[b]
ARDS	8 (2.4)	8 (5.4)	0 (0.0)	**0.001**[b]
NSTEMI	19 (5.7)	6 (4.1)	13 (6.9)	0.185
Sepsis	15 (4.5)	14 (9.5)	1 (7.0)	**< 0.001**[b]
MODS	24 (7.2)	24 (16.3)	0 (0.0)	**< 0.001**[b]
Length of hospitalization (days)				
Median (IQR)	7 (4-12)	8 (4-14)	6 (4-9)	0.064[b]

ARDS: Acute respiratory distress syndrome; NSTEMI: Non-ST elevated myocardial infarction; MODS: Multiple Organ Dysfunction Syndrome; NP: Nasal Prong; FM: Face mask; HFNC: High Flow Nasal Cannula; IQR: Interquartile range; *p* values were determined using a Pearson Chi-squared test; b Fisher's Exact test, and c Mann-Whitney U test.

dysfunction syndrome (MODS) ($p < 0.001$) between death and recovered groups. Furthermore, there was a significant difference in terms of duration of hospitalization ($p < 0.001$) between dead and recovered patients, as shown in Table 3.

Predictors of mortality

Demographic, clinical characteristics and treatment were initially evaluated using the Chi-squared test, Mann Whitney U test (Tables 1-3). Then the variables with a significance of $p < 0.20$ or relevant to the literature (gender, diabetes mellitus, cardiovascular disease, chronic kidney disease) were analyzed using a backward multivariate logistic regression. Multivariate logistic regression revealed that patients aged ≥ 65 years old increase their odds of mortality by 20.89 times (aOR 20.89, 95% CI 5.81-75.15), while a one-unit increase in serum creatinine and pulse rate increases mortality by 3% (aOR 1.03, 95% CI 1.01-1.63) and 34% (aOR 1.34, 95%CI 1.11-1.63), respectively. Regarding treatment, antibiotics, corticosteroids, ACEI/ARB, and Oxygen supply through HFNC, NMV, and IMV increase the odds of mortality by 3.40 (95% CI: 1.29-8.98), 49.68 (95% CI: 1.83-1350.31), 0.12 (95% CI: 0.027-0.518), 13.08 (95% CI: 1.70-100.54), 229.01 (95% CI: 29.30-1789.71), and 379.54 (95% CI: 36.60-3935.87), respectively. On the other hand, patients who received ACEI/ARB had an 88% lower risk of mortality than those who did not receive ACEI/ARB (aOR 0.12, 95% CI 0.027-0.52), after adjusting other variables, as shown in Table 4.

Discussion

Given that HTN is amongst the most prevalent comorbid illnesses affecting individuals of any age, concordant findings indicate the need for further investigations focusing on understanding the specific risks associated with mortality in COVID-19-infected

Table 4. Multivariate analysis of predictors of mortality among hypertensive COVID-19 patients.

Variable	Adjusted OR (95% CI)	*p value*
Age ≥ 65 years	20.89 (5.81-75.15)	**< 0.001**
Pulse rate	1.03 (1.01-1.63)	**0.006**
Serum creatinine	1.34 (1.11-1.63)	**0.002**
Antibiotics (Yes)	3.40 (1.29-8.98)	**0.014**
Corticosteroids (Yes)	49.68 (1.83-1350.31)	**0.020**
ACEI/ARB (Yes)	0.12 (0.03-0.52)	**0.005**
O_2 supply HFNC (Yes)	13.08 (1.70-100.54)	**< 0.001**
NMV (Yes)	229.01 (29.30-1789.71)	**< 0.001**
IMV (Yes)	379.54(36.60-3935.87)	**< 0.001**

aOR: Adjusted odd ratio; CI: Confidence interval; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; NMV: Non-invasive mechanical ventilation; IMV: Invasive mechanical ventilation.

patients with hypertension to identify the strategies to mitigate these risks. Therefore, the current study aims to determine the predictor of mortality among COVID-19 patients with HTN by comparing the general characteristics, clinical presentation, treatment, and complications among dead and recovered COVID-19 patients with HTN, during the third and fourth waves in Karachi, Pakistan.

According to the findings, 42.09% of all hospitalized COVID-19 patients had HTN, supported by previous studies conducted in Iran (40.2%) [29] and Italy (42.9%) [30]. However, other studies reported a disproportionated prevalence of HTN at 15% in China [10], 56.6% in the United States [31], and 81.7% in Albania [32]. Moreover, the in-hospital mortality rate (44.7%) of hypertensive COVID-19 patients in our study population was higher than in China in 2020 [33].

The mortality of hypertensive COVID-19 patients is related to the factors mentioned in Table 1-3. A study by Alizadehsani *et al.* (2022) presented a slightly higher ratio of male COVID-19 patients with CVD (56.6%) [29]. On the contrary, our study reflects a higher proportion of COVID-19 patients with HTN as females (54.7%). It can be attributed to the greater prevalence of HTN in females than in males [34]. Besides, sampling methods, geography, variations in lifestyle, and diet could contribute to the higher prevalence of HTN among females [35]. Moreover, aging, obesity, co-existence of diabetes, and excessive use of salty, caloric, and fatty food may contribute to a higher prevalence of hypertension in females [36].

Previous studies have shown that patients aged < 65 are more affected by COVID-19 [37-39]. Following the studies, most patients in our study fell into the same age group. In our study, the median age of the patients who died due to COVID-19 was 65 (57-72) years. However, a study on 410 COVID-19 patients from Milan, Italy, reported a significantly higher median age of fatal cases of COVID-19 was 76 (67–82) years. It is possible because of compromised lung function and vulnerability to respiratory illnesses with natural lung aging in older patients [40]. Additionally, studies have described that geriatric patients are more vulnerable to developing acute respiratory distress syndrome [41] because of the gradual decline of both the innate immune system, which leads to decreased ability to clear off pathogens, and the adaptive immune system's ability to produce antibodies against antigens [42].

Besides HTN, 57.1% of the patients in the deceased cohort had diabetes; however, there was no strong correlation with mortality. The findings of Elrayees *et al.* suggested a comparatively lower prevalence of combined diabetes and hypertension (33.0%) among COVID-19 patients [43]. However, Elrayees *et al.* did not observe any significant severity difference among these patients. This may be due to the co-existence of DM and HTN in the population of Pakistan [34].

Regarding baseline blood pressure, we determined that despite pre-existing hypertension among COVID-19 patients, the median blood pressure was 140/80 mm Hg, possibly due to past antihypertensive therapy. Consistent with our findings, a few studies suggested the median blood pressures were 140/83 mm Hg [44] and 134/76 mm Hg [45]. Our study revealed that shortness of breath, fever, weakness, and baseline respiratory rate, were significantly associated with mortality, and baseline oxygen saturation was substantially lower in patients who died of COVID-19. This is attributed to progressive hypoxia, a critical pointer to the severity and poor prognosis of COVID-19 [37]. In addition, our study discovered that patients who died had raised total leucocytes (leukocytosis) and neutrophils (neutrophilia), and most of the patients received antibiotic therapy for co-infections (bacterial or fungal) in the deceased patients. Moreover, lymphocyte count decreased during the acute stage of infection, supported by Huang *et al.* [37]. Evidence shows that lymphocytes are either consistently consumed or insufficiently regenerated during viral infections [46]. Our study also revealed elevated serum ferritin levels, high sensitivity troponin-I, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, and procalcitonin in patients who died compared to recovered ones. It is supported by the studies conducted by Basu *et al.* [47] and Chan *et al.* [48], as these inflammatory markers are known to be associated with the severity of COVID-19 patients [43]. However, some are considered to indicate inflammation or sepsis, and others are consistent with cytokine release syndrome (CRS) [49].

Previously, two studies identified factors that may predict mortality in COVID-19 patients. One study found that elevated levels of creatinine kinase and lactate dehydrogenase were associated with an increased risk of death [32], while another study identified older age, cerebrovascular or cardiovascular disease, low levels of CD3 + CD8 + T-cells, and high levels of cardiac troponin I as the potential predictors of mortality among hospitalized patients with COVID-19 [39]. In contrast, our study focused specifically on hypertensive patients with COVID-19 and suggested that older age, elevated pulse rate and serum creatinine, use of antibiotics, corticosteroids, and need for NMV

and IMV were the significant predictors of mortality among hypertensive COVID-19 patients.

The standard treatment for the management of severe and critical cases in Pakistan includes antiviral (Remdesivir), steroids (Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisone), anticoagulants (Enoxaparin, Heparin), antibiotics (in case of suspected bacterial co-infection) multiple vitamins (Vitamin B, C, D), and Tocilizumab for patients who fail to respond steroids and worsen [50]. Regarding the treatment, antibiotics, antifungal, and corticosteroid therapies were consumed more in the patients from the death group than in the recovered group; similar findings were reported by Deng *et al.* [38] and Nasir *et al.* [51] in their research. It may be suggestive that deceased patients might have other co-existing and hospital-acquired infections caused by *E. coli, K. pneumoniae, A. baumannii* [52], and fungal infections, which may further increase the risk of mortalities among COVID-19 patients [38,53].

Regarding antihypertensive therapy, in line with our findings, McFarlane *et al.* [45], Zhang *et al.* [54], and Gao *et al.* [18] also reported that consumption of ACEIs/ARBs was related to reduced mortality risk. Our findings also suggested that patients who received ACEI/ARB during hospitalization had a 79.6% lower mortality risk than those who did not receive ACEI/ARB. The plausible mechanism linked with ACEI/ARB could be a decrease in the release of inflammatory markers (CRP and D-Dimers) by interacting with the RAAS pathway, thus improving clinical outcomes [55-57]. We also observed that the mortal cases were substantially associated with complications such as cardiac arrest, ARDS, sepsis, MODS, need for mechanical ventilation (non-invasive and invasive). Several studies have also reported similar risk factors associated with mortality [58-60]. Our study suggests a longer duration of hospitalization in the death cohort, supported by the study of Liu *et al.* [61]. This may be due to the discharge protocol of the hospital [62]. However, in contrast to our findings, the length of hospital stay was significantly higher in the recovered group compared to the death group in previous studies [30,38].

The findings from our study extend the previous research of equivocal or potentially confounded associations of HTN with COVID-19 illness [63]. Furthermore, our results point to persistence and even highlight demographic and clinical risk factors during the third and fourth waves of COVID-19, which are characterized by a more transmissible but generally less virulent strain of the virus. However, there are several limitations to our study that warrant consideration. Firstly, we performed a single-centered study; therefore, the findings cannot be generalized to represent the rest of the country. In addition, observational studies are subject to selection bias due to smaller sample sizes. Secondly, there was insufficient data on the past medication history of blood pressure, making it difficult to differentiate between recently diagnosed HTN and chronic HTN and to compare patients on ACEI/ARB with those on non-ACEI/ARB therapy. Thus, it is unclear whether the protective effect of the RAAS blocker observed in our study was due to short-term use during hospitalization or chronic use before admission. Further studies comparing large cohorts of patients on ACEI/ARB vs non-ACEI/ARB antihypertensive drugs are needed to address these limitations and confirm the protective effect of ACEI/ARB among COVID-19 patients with hypertension. Finally, due to the limited sample size, some key predictors such as blood glucose levels, and antidiabetic therapy may have been missed or not identified sufficiently. Therefore, future studies are warranted to further investigate and validate the predictors among large population.

Conclusions

Our study concluded that older age (≥ 65 years), pulse rate, serum creatinine, antibiotics use, need for oxygen supplements, non-invasive mechanical ventilation, and invasive mechanical ventilation were predictors of death among hypertensive COVID-19 patients during third and fourth waves in Pakistan. There was a significant difference while comparing age, baseline severity, vital signs, laboratory finding, treatment, and complications between death and recovery groups. The findings might help healthcare providers to identify vulnerable patients and take further preventive measures

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Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

Supplementary Table 1. History of antihypertensive therapy (N=333).

Variables	N (%)
Compliance towards antihypertensive	164 (49.2)
CCB	79 (23.7)
ARB	60 (18.0)
BB	49 (14.7)
Diuretics	43 (12.9)
ACEI	24 (7.2)

ACEI: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blockers, CCB: Calcium channel blocker, BB: Beta blockers.