ORIGINAL ARTICLE

# Characteristics and Factors Associated with Mortality of 200 COVID-19 Patients at a Philippine COVID-19 Tertiary Referral Center

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## ABSTRACT

**Objectives.** To describe the clinical profile and factors associated with mortality among the first 200 patients confirmed to have COVID-19 infection admitted in the University of the Philippines – Philippine General Hospital (UP-PGH).

**Methodology.** We conducted a review of adult patients with confirmed COVID-19 infection admitted to the UP-PGH, a designated COVID-19 referral center. Demographic, clinical data and clinical outcomes were extracted from medical records. Frequencies and distributions of various clinical characteristics were described, and factors associated with mortality were investigated.

**Results.** Of the 200 patients in our cohort, most were male (55.5%), and the median age was 56 years old. Underlying comorbid illnesses were present in 67.5% of patients, which included hypertension (49.5%), diabetes mellitus (26.5%), and other cardiovascular diseases (20.5%). The most frequent presenting symptoms were cough (69.0%), fever (58.5%), or shortness of breath (53.0%). Most patients presented with mild (n=41, 20.5%) to moderate illness (n=99, 49.5%) and only 60 were considered severely (n=32, 16.0%) or critically ill (n=28, 14.0%). Many (61%) received empiric antibiotics, while 44.5% received either repurposed drugs or investigational therapies for COVID-19. Bacterial co-infection was documented in 11%, with *Klebsiella pneumoniae* commonly isolated. In-hospital mortality was 17.5%, which was highest for critical COVID-19 (71.4%). Mortality was observed to be higher among patients aged 60 and above, requiring oxygen, ventilatory support, and ICU admission, and those who developed acute kidney injury, acute stroke, sepsis, and nosocomial pneumonia.

**Conclusion.** Our study confirmed that COVID-19 affects older individuals and those with underlying comorbid conditions. Empiric antimicrobial treatment was given for most patients, despite documentation of bacterial infection in only 11%. *K. pneumoniae* was commonly isolated, reflecting local epidemiology. The mortality rate during this early period of the pandemic was high and comparable with other institutions. Factors associated with mortality were related to critical COVID-19 and were similar to other studies.

*Key Words: COVID-19, Philippines, epidemiology, mortality*

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has resulted in a significant global pandemic affecting more than 92 million people worldwide with over 1,995,037 deaths based on a report published by the World Health Organization (WHO) on January 16, 2021.[1] In the Philippines, the first case was reported on January 30, 2020, with local transmission documented on March 7, 2020. The number of confirmed cases in the country has rapidly increased since then, and

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as of January 16, 2021, there were 496,691 confirmed cases and 9,884 deaths recorded.[2]

There is limited published data on the epidemiology and clinical outcomes of COVID-19 patients in the Philippines. With the emergence of new variants of SARS-CoV-2, there is a need to establish the epidemiologic and clinical characteristics of patients with COVID-19 caused by the virus's earlier variant.[3] This study aimed to describe the clinical profile and determine the factors associated with mortality among the first 200 confirmed COVID-19 patients admitted at the University of the Philippines - Philippine General Hospital (UP-PGH), a tertiary hospital in the Philippines. The UP-PGH was designated as a COVID-19 hospital and converted into a referral center by March 20, 2020.

## METHODS

### Study Participants

This study included the first 200 adult patients aged 19 years old and above, with RT-PCR-confirmed COVID-19, admitted at UP-PGH from March 12, 2020, to April 28, 2020. Patients who died within 24 hours of admission were excluded.

### Study Design

A descriptive retrospective cohort design was employed. Demographic, clinical, laboratory, treatment, and outcome data were extracted from paper and electronic medical records [e.g., Registry of Admissions and Discharges (RADISH), PGH Medical Record System (OpenMRS)] using a standardized data collection form. All data gathered in the study were stored in a Microsoft Excel worksheet. Radiologists in the study team reviewed digital x-ray images. The University of the Philippines-Manila review board approved this retrospective study (UPMREB CODE 2020-285-01), including a waiver of patient informed consent.

### Variables and Outcomes

Study variables were collected and included age, sex, comorbid illnesses, symptoms on presentation, baseline vital signs, radiographic, and diagnostic tests. The density of radiographic findings was described as ground glass, consolidation, reticular, nodular, or fibrotic. Ground glass opacities in chest radiographs were defined as haziness of the lung parenchyma, preserving the bronchovascular margins.[4] Status on admission [e.g., need for oxygen, ventilatory support, vasopressor, or presence of acute respiratory distress syndrome (ARDS)], and antibiotics and investigational therapies received, including hydroxychloroquine/chloroquine (HCQ/CQ), lopinavir/ritonavir (LPV/r), tocilizumab, convalescent plasma, and hemoperfusion were also recorded.

The severity of COVID-19 illness was classified based on the Philippine Society for Microbiology and Infectious Diseases (PSMID) guidelines as follows: *mild* - patients with symptoms consistent with COVID-19 but without evidence of pneumonia; *moderate* - patients with clinical and radiographic evidence of pneumonia, but not requiring oxygen; *severe* - patients with clinical and radiographic evidence of pneumonia with oxygen saturation <92% on room air, and requiring oxygen support; *critical* - patients with COVID-19 with ARDS, septic shock, requiring mechanical ventilation, admission to the intensive care unit (ICU) or both.[5]

Clinical events recorded included: oxygen supplementation, ventilatory support, ARDS, ICU admission, acute kidney injury (AKI), renal replacement therapy (RRT), acute stroke, acute myocardial infarction, sepsis and septic shock, and nosocomial infections such as hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), catheter-related bloodstream infection (CRBSI), and catheter-associated urinary tract infections (CAUTI). Clinical outcomes of in-hospital death (i.e., non-survival) and discharge (i.e., survival) were the primary outcomes of interest.

### Statistical Analysis

We used descriptive statistics and determined frequency distributions of demographic and clinical characteristics. Shapiro-Wilk test was used to assess the normality of continuous data. Variables were compared using chi-square for categorical variables and the Mann-Whitney U test for continuous variables. All tests were two-tailed, with a p-value less than 0.05 considered statistically significant. Analyses were conducted using Microsoft Excel and MedCalc version 19.7.4.

## RESULTS

### Characteristics of the Study Cohort

Of the first 200 cases, 111 (55.5%) were male, with a median age of 56 (IQR 42 to 67) years. On admission, most patients presented with mild (n=41, 20.5%) to moderate illness (n=99, 49.5%) and only 60 were considered severely (n=32, 16.0%) or critically ill (n=28, 14.0%). Majority of patients (n=135, 67.5%) had at least one co-morbid illness, the most common being hypertension (n=99, 49.5%), diabetes mellitus (DM) (n=53, 26.5%), and cardiovascular disease including heart failure and ischemic heart disease (n=41, 20.5%). Of the cohort, only a few had chronic kidney disease (n=20, 10%), chronic obstructive pulmonary disease (COPD) (7, 3.5%), bronchial asthma (n=13, 6.5%), or active tuberculosis (n=10, 5%). There was no statistically significant difference between the proportion of survivors and non-survivors with co-morbid illness [107/165 (64.8%) vs. 28/35 (80.0%), p = 0.124] but the presence of neurologic disease was more common among non-survivors than survivors [6/35 (17.1%) vs. 8/135 (4.8%), p=0.010]. Co-existing neurologic diseases in the cohort included history of stroke (n=10), Parkinson's disease (n=2), and seizure disorders (n=2). Of the 6 who died, 5 had prior ischemic stroke and 1 had seizure disorder. A summary of baseline demographic data is in Table 1.

**Table 1.** Demographic and clinical profile of patients with COVID-19 admitted in UP-PGH

| | Overall (N=200) | | Clinical Outcome | | | | |
|---|---|---|---|---|---|---|---|
| | | | Survivor (N=165) | | Nonsurvivor (N=35) | | P-value |
| ***Age*** | | | | | | | |
| Median, IQR | 56 | (42 to 67) | 54 | (40 to 63) | 67 | (60 to 77) | <0.001 |
| Less than 60 years, No. (%) | 116 | (58.0) | 108 | (65.5) | 8 | (22.9) | |
| 60 years and above, No. (%) | 84 | (42.0) | 57 | (34.5) | 27 | (77.1) | <0.001 |
| ***Sex, No. (%)*** | | | | | | | |
| Male | 111 | (55.5) | 92 | (55.8) | 19 | (54.3) | |
| Female | 89 | (44.5) | 73 | (44.2) | 16 | (45.7) | 0.873 |
| ***Coexisting Condition, No. (%)*** | | | | | | | |
| Diabetes mellitus | 53 | (26.5) | 41 | (24.8) | 12 | (34.3) | 0.250 |
| Hypertension | 99 | (49.5) | 80 | (48.5) | 19 | (54.3) | 0.533 |
| Heart disease | 41 | (20.5) | 34 | (20.6) | 7 | (20.0) | 0.936 |
| Chronic kidney disease | 20 | (10.0) | 14 | (8.5) | 6 | (17.1) | 0.121 |
| COPD | 7 | (3.5) | 5 | (3.0) | 2 | (5.7) | 0.433 |
| Asthma | 13 | (6.5) | 12 | (7.3) | 1 | (2.9) | 0.336 |
| Active pulmonary tuberculosis | 10 | (5.0) | 7 | (4.2) | 3 | (8.6) | 0.286 |
| HIV | 2 | (1.0) | 2 | (1.2) | 0 | (0) | 0.513 |
| Cancer | 13 | (6.5) | 9 | (5.4) | 4 | (11.4) | 0.193 |
| Neurologic disease | 14 | (7.0) | 8 | (4.8) | 6 | (17.1) | 0.010 |
| Smoker | 36 | (18.0) | 30 | (18.2) | 6 | (17.1) | 0.884 |

## Signs and symptoms

Majority of patients (n=199, 99.5%) were symptomatic. The most common symptom was cough (n=138, 69.0%), followed by fever (n=117, 58.5%), and shortness of breath (n=106, 53.0%). Gastro-intestinal symptoms such as diarrhea (n=53, 26.5%), nausea (n=2, 1.0%) and vomiting (n=3, 1.5%) occurred less commonly. Sore throat [50 (30.3%) vs. 2 (5.71%), p=0.003], and myalgias [26 (15.8%) vs. 1 (2.9%), p=0.042] were more common among survivors (n=165), while shortness of breath [78 (47.3%) vs. 28 (80%), p<0.001] and decreased sensorium [4 (2.4%) vs. 12 (34.3%), p<0.001] were more common among non-survivors (Table 2). Median time from symptom onset to hospital admission was 10 days (IQR 6 to 14), and was not significantly different between survivors and nonsurvivors (p = 0.084).

Upon admission, 41% of the patients (n=82) required oxygen support. Non-survivors had higher median heart rate, respiratory rate, temperature, lower peripheral oxygen

**Table 2.** Clinical presentation of patients admitted with COVID-19 infection admitted in UP-PGH

| | Overall (N=200) | | Clinical Outcome | | | | |
|---|---|---|---|---|---|---|---|
| | | | Survivor (N=165) | | Nonsurvivor (N=35) | | P-Value |
| ***Presenting Symptoms, No. (%)*** | | | | | | | |
| Headache | 9 | (4.5) | 8 | (4.8) | 1 | (2.9) | 0.606 |
| Chills | 6 | (3.0) | 6 | (3.6) | 0 | (0) | 0.252 |
| Fever | 117 | (58.5) | 97 | (58.8) | 20 | (57.1) | 0.858 |
| Cough | 138 | (69.0) | 114 | (69.1) | 24 | (68.6) | 0.952 |
| Rhinorrhea/congestion | 33 | (16.5) | 29 | (17.6) | 4 | (11.4) | 0.373 |
| Shortness of breath | 106 | (53.0) | 78 | (47.3) | 28 | (80.0) | <0.001 |
| Sore throat | 52 | (26.0) | 50 | (30.3) | 2 | (5.7) | 0.003 |
| Malaise/fatigue/generalized weakness | 54 | (27.0) | 43 | (26.1) | 11 | (31.4) | 0.660 |
| Myalgia | 27 | (13.5) | 26 | (15.8) | 1 | (2.9) | 0.042 |
| Diarrhea | 53 | (26.5) | 44 | (26.7) | 9 | (25.7) | 0.908 |
| Nausea | 2 | (1.0) | 2 | (1.2) | 0 | (0) | 0.513 |
| Vomiting | 3 | (1.5) | 2 | (1.2) | 1 | (2.9) | 0.467 |
| Decreased appetite | 18 | (9.0) | 13 | (7.9) | 5 | (14.3) | 0.229 |
| Decreased sensorium | 16 | (8.0) | 4 | (2.4) | 12 | 34.3) | <0.001 |
| ***Vital Signs on Admission, median (IQR)*** | | | | | | | |
| Systolic blood pressure (mmHg) | 130 | (115 to 140) | 130 | (118 to 140) | 130 | (107 to 153) | 0.758 |
| Diastolic blood pressure (mmHg) | 80 | (70 to 89) | 80 | (70 to 89) | 72 | (60 to 80) | 0.136 |
| Mean arterial pressure (mmHg) | 93 | (84 to 104) | 93 | (87 to 105) | 94 | (78 to 102) | 0.389 |
| Heart rate (beats/min) | 87 | (78 to 97) | 85 | (77 to 92) | 101 | (85 to 119) | <0.001 |
| Respiratory rate (breaths/min) | 20 | (19 to 24) | 20 | (19 to 22) | 25 | (21 to 30) | <0.001 |
| Temperature (degrees Celsius) | 36.7 | (36.3 to 37.0) | 36.7 | (36.2 to 36.9) | 36.8 | (36.5 to 37.4) | 0.003 |
| Peripheral oxygen saturation (%) | 97 | (94 to 98) | 97 | (95 to 99) | 94 | (88 to 97) | <0.001 |
| Glasgow Coma Score | 15 | (15) | 15 | (15) | 15 | (11 to 15) | <0.001 |

**Table 2.** Clinical presentation of patients admitted with COVID-19 infection admitted in UP-PGH *(continued)*

| | Overall (N=200) | | Clinical Outcome | | | | |
|---|---|---|---|---|---|---|---|
| | | | Survivor (N=165) | | Nonsurvivor (N=35) | | P-Value |
| ***Laboratory Findings on Admission*** | | | | | | | |
| Complete Blood Count, median (IQR) | | | | | | | |
| Hemoglobin | 133.0 | (117.0 to 144.0) | 136.0 | (122.0 t0 146.2) | 117.0 | (88.7 to 140.0) | <0.001 |
| Hematocrit | 40.0 | (36.0 to 43.7) | 41.0 | (37.0 to 44.0) | 36.0 | (26.7 to 42.0) | 0.003 |
| White blood cells | 7.4 | (5.6 to 10.7) | 7.2 | (5.6 to 9.4) | 11.3 | (5.4 to 16.7) | 0.002 |
| Neutrophil | 67.0 | (59.0 to 78.7) | 65.0 | (58.0 to 73.2) | 86.0 | (74.2 to 91.0) | <0.001 |
| Lymphocyte | 22.0 | (13.0 to 29.0) | 24.0 | (15.0 to 30.0) | 7.0 | (4.0 to 14.7) | <0.001 |
| Absolute lymphocyte count | 1472.0 | (1028.5 to 2138.5) | 1534.0 | (1470.0 to 1733.5) | 791.0 | (541.0 to 1381.5) | <0.001 |
| Neutrophil lymphocyte ratio | 3.1 | (2.0 to 6.1) | 2.6 | (2.0 to 4.9) | 12.3 | (5.2 to 23.7) | <0.001 |
| Platelet | 269.5 | (182.2 to 330.0) | 283.0 | (195.0 to 339.0) | 235.0 | (139.2 to 284.5) | 0.015 |
| Arterial blood gas, median (IQR) | | | | | | | |
| pH | 7.42 | (7.39 to 7.45) | 7.42 | (7.40 to 7.45) | 7.41 | (7.38 to 7.44) | 0.286 |
| $pCO_2$ | 33.2 | (28.3 to 38.0) | 34.0 | (29.8 to 38.0) | 28.0 | (25.6 to 35.6) | 0.018 |
| $PaO_2$ | 87.0 | (73.0 to 99.9) | 88.5 | (74.1 to 99.4) | 80.4 | (68.2 to 100.9) | 0.477 |
| $HCO_3$ | 22.0 | (19.1 to 24.2) | 22.3 | (20.0 to 24.2) | 19.1 | (17.3 to 23.2) | 0.006 |
| $O_2$ saturation | 97.0 | (94.7 to 98.0) | 97.0 | (94.8 to 98.0) | 95.9 | (92.0 to 98.3) | 0.351 |
| $PaO_2$ and $FiO_2$ ratio | 382.4 | (269.3 to 456.9) | 396.9 | (302.1 to 457.6) | 230.0 | (110.3 to 378.4) | <0.001 |
| Blood Chemistry, median (IQR) | | | | | | | |
| BUN (mmol/L) | 4.8 | (3.5 to 7.8) | 4.5 | (3.4 to 6.0) | 12.0 | (5.7 to 21.2) | <0.001 |
| Serum creatinine (µmol/L) | 76.0 | (59.0 to 111.0) | 72.0 | (58.0 to 91.5) | 147.0 | (88.5 to 205.2) | <0.001 |
| AST (U/L) | 42.0 | (30.2 to 70.7) | 40.0 | (29.2 to 62.7) | 63.0 | (37.7 to 78.0) | 0.024 |
| ALT (IU/L) | 36.0 | (20.0 to 61.5) | 40.0 | (22.0 to 63.0) | 26.0 | (18.2 to 50.5) | 0.092 |
| albumin (g/L) | 38.0 | (33.0 to 43.0) | 39.0 | (33.0 to 45.0) | 33.0 | (30.0 to 38.0) | <0.001 |
| Total bilirubin ((mg/dl) | 0.71 | (0.52 to 0.98) | 0.70 | (0.52 to 0.95) | 0.81 | (0.49 to 1.09) | 0.595 |
| Direct bilirubin (mg/dl) | 0.26 | (0.19 to 0.39) | 0.25 | (0.18 to 0.35) | 0.39 | (0.30 to 0.62) | <0.001 |
| Indirect bilirubin (mg/dl) | 0.43 | (0.26 to 0.62) | 0.44 | (0.29 to 0.63) | 0.31 | (0.13 to 0.56) | 0.055 |
| LDL (mg/dl) | 106.3 | (78.3 to 144.8) | 120.9 | (84.3 to 148.8) | 89.3 | (46.9 to 111.2) | 0.047 |
| Triglyceride (mg/dl) | 133.0 | (106.2 to 204.4) | 131.4 | (102.6 to 194.0) | 162.8 | (115.5 to 265.3) | 0.326 |
| Inflammatory Markers, median (IQR) | | | | | | | |
| LDH (U/L) | 280.0 | (208.0 to 425.5) | 259.0 | (203.0 to 379.0) | 481.0 | (391.0 to 765.0) | <0.001 |
| Serum ferritin (ng/mL) | 452.0 | (193.0 to 1250.0) | 370.5 | (173.5 to 841.5) | 1510.0 | (570.1 to 2927.5) | <0.001 |
| Serum procalcitonin (ng/mL) | 0.07 | (0.04 to 0.37) | 0.05 | (0.04 to 0.24) | 1.23 | (0.36 to 5.05) | <0.001 |
| D-dimer (ug/mL) | 0.96 | (0.38 to 3.15) | 0.49 | (0.32 to 1.17) | 12.09 | (1.41 to 19.72) | <0.001 |
| C-reactive protein, No. (%) | | | | | | | |
| ≤12 mg/L | 66 | (33.0) | 64 | (38.8) | 2 | (5.7) | |
| >12 mg/L | 108 | (54.0) | 81 | (49.1) | 27 | (77.1) | <0.001 |
| ***Illness Severity on Admission, No. (%)*** | | | | | | | |
| Mild | 41 | (20.5) | 41 | (24.8) | 0 | (0) | <0.001 |
| Moderate | 99 | (49.5) | 92 | (55.8) | 7 | (20.0) | |
| Severe | 32 | (16.0) | 24 | (14.6) | 8 | (22.9) | |
| Critical | 28 | (14.0) | 8 | (4.8) | 20 | (57.1) | |
| ***Status on Admission, No (%)*** | | | | | | | |
| Requiring oxygen support | 82 | (41.0) | 52 | (31.5) | 30 | (85.7) | <0.001 |
| On ventilatory support | 15 | (7.5) | 4 | (2.4) | 11 | (31.4) | <0.001 |
| Acute respiratory distress syndrome | 49 | (24.5) | 25 | (15.1) | 24 | (68.6) | <0.001 |
| On vasopressor | 4 | (2.0) | 0 | (0) | 4 | (11.4) | <0.001 |

saturation, and lower Glasgow Coma Score. A more significant proportion of non-survivors needed oxygen, mechanical ventilation, and vasopressor support upon admission. A more significant proportion of non-survivors already had ARDS upon admission. Table 2 shows the summary of these findings.

## Diagnostic Tests

All patients had a baseline complete blood count (CBC) on admission. Overall median hemoglobin was 133 (IQR 117 to 114); mean white blood cell count (WBC) and absolute lymphocyte count (ALC), 7.4 $x10^9$ cells/L (IQR 5.6 to 10.7), and 1472 $x10^9$ cells/L (IQR 1028.5 to 2138.5), respectively. The median neutrophil to lymphocyte ratio was 3.1 (IQR 2.0 to 6.1).

Inflammatory markers were frequently evaluated at baseline. Average procalcitonin (n= 162), ferritin (n=195), and lactate dehydrogenase (LDH) (n=196) were 0.07 ng/ml (IQR 0.04 to 0.37), 452 ng/ml (IQR 193 to 1250), and 280 U/L (IQR 208 to 425), respectively. More than half (n=108, 54%) had elevated C-reactive protein (CRP) levels of >12 mg/dL. D- dimer was only evaluated in 50 patients but was elevated with a median of 0.96 mcg/ml (IQR 0.38 to 3.15).

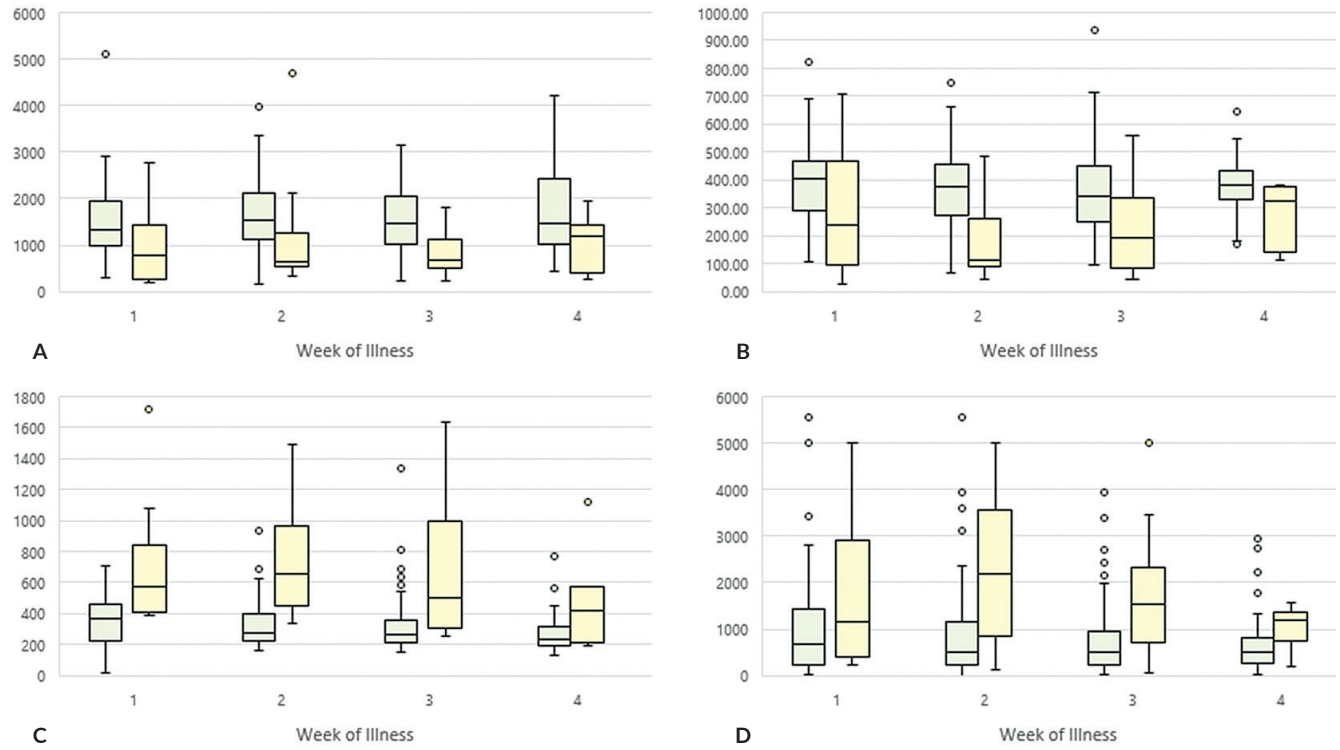


**Figure 1.** Comparing the different laboratory findings between COVID-19 survivors *(green)* and non-survivors *(yellow)* throughout the illness. Boxes span the IQR with median values indicated by a horizontal bar. Circles represent outliers. **(A)** Absolute Lymphocyte Count ($10^9$ cells/L), lymphopenia corresponds to ALC <1,000; **(B)** $PaO_2/FiO_2$ ratio, hypoxemia corresponds to P/F ratio <300; **(C)** Serum Lactate dehydrogenase (U/L); **(D)** Serum Ferritin (ng/mL).

A baseline arterial blood gas (ABG) was available for nearly all patients (n=197), with a median pH of 7.42 (IQR 7.39 to 7.45), $PaO_2$ 87 (IQR 73.0 to 99.9), and $O_2$ saturation 97 (94.7 to 98.0). The Median $PaO_2/FiO_2$ ratio (PFR) on admission was 382.4 (269.3 to 456.9). A complete list of laboratory tests is in Table 2.

Comparing the median levels of ALC, PFR, LDH, and serum ferritin levels throughout illness between survivors and non-survivors is shown in Figure 1.

Admission chest radiographs were obtained in 198 patients, showing infiltrates in the majority (136/198, 68.7%). Among patients with infiltrates, infiltrates were bilateral (55.6%), diffuse (40.4%), and seen in both the central and peripheral areas of the lungs in about half of cases (48.0%). The density of the infiltrates was described as having a ground-glass character in 51.0% of patients. A greater proportion of non-survivors had bilateral infiltrates [28 of 34 (82.3%) vs. 82 of 164 (50.0%)]. More non-survivors also had extensive infiltrates occupying more than 50% of the lung area [19 (54.3%) vs. 48 (29.3%)]. Table 3 shows the radiographic findings of patients with COVID-19 pneumonia.

## Antimicrobial use

The majority of patients [122 (61%)] received empiric antibiotics on admission – 6/41 patients with mild, 60/99 with moderate, 28/32 with severe, and all patients (n=28) with the critical disease received empiric antibiotics.

One hundred forty-nine patients (74.50%) received antibiotics at any time during their admission. Azithromycin was the most used antibiotic (n=96, 48%), followed by penicillins (n=88, 44%) and cephalosporins (n=72, 36%). Azithromycin was administered to 14.6% of patients with mild disease, 54.5% of patients with moderate disease, 56.2% with severe disease, and 60% of patients with the critical disease. Patients with the mild disease received antimicrobials from the fewest drug classes. Compared to survivors, a bigger proportion of non-survivors received agents from nearly all antibiotic classes. Table 4 summarizes antibiotic use in the patient cohort.

## Use of investigational drugs and therapies

Nearly half (n=89, 44.5%) of patients in the cohort received repurposed drugs or investigational therapies such as HCQ/CQ (n=54), LPV/r (n=16), tocilizumab (n=24), convalescent plasma (n=7), and hemoperfusion (n=6). Most patients with severe (26 of 32) and critical disease (20 of 28) received any or a combination of these therapies, while less than half of the moderate cases (42 of 99) and only 1 of 41 mild cases did. Tocilizumab was often used combined with other investigational therapies and given to patients with severe to critical disease. Convalescent plasma and

**Table 3.** Chest radiographic findings of patients with COVID-19 pneumonia admitted in UP-PGH

| Radiographic Findings | Overall (N=198) | | Clinical Outcome | | | |
|---|---|---|---|---|---|---|
| | | | Survivor (N=164) | | Nonsurvivor (N=34) | |
| ***Regional Involvement, No. (%)*** | | | | | | |
| Unilateral | 26 | (13.1) | 22 | (13.4) | 4 | (11.8) |
| Bilateral | 110 | (55.6) | 82 | (50.0) | 28 | (82.3) |
| ***Craniocaudal Distribution, No. (%)*** | | | | | | |
| Upper | 3 | (1.5) | 3 | (1.8) | 0 | (0) |
| Upper-mid | 3 | (1.5) | 3 | (1.8) | 0 | (0) |
| Middle | 3 | (1.5) | 3 | (1.8) | 0 | (0) |
| Mid-lower | 30 | (15.1) | 24 | (14.6) | 6 | (17.6) |
| Lower | 11 | (5.6) | 9 | (5.5) | 2 | (5.9) |
| Upper and lower | 6 | (3.0) | 5 | (3.0) | 1 | (2.9) |
| Diffuse | 80 | (40.4) | 57 | (34.8) | 23 | (67.6) |
| ***Transverse Distribution, No. (%)*** | | | | | | |
| Peripheral | 26 | (13.1) | 22 | (13.4) | 4 | (11.8) |
| Central | 15 | (7.6) | 9 | (5.5) | 6 | (17.6) |
| Both | 95 | (48.0) | 73 | (44.5) | 22 | (64.7) |
| ***Density, No. (%)*** | | | | | | |
| Ground glass | 101 | (51.0) | 81 | (49.4) | 20 | (58.8) |
| Consolidation | 38 | (19.2) | 28 | (17.1) | 10 | (29.4) |
| Nodular | 20 | (10.1) | 14 | (8.5) | 6 | (17.6) |
| Reticular | 3 | (1.5) | 3 | (1.8) | 0 | (0) |
| Fibrotic | 1 | (0.5) | 1 | (0.6) | 0 | (0) |
| ***Extent, No. (%)*** | | | | | | |
| No Infiltrates | 62 | (31.3) | 60 | (36.6) | 2 | (5.9) |
| <25% | 31 | (15.7) | 27 | (16.5) | 4 | (11.8) |
| 25-50% | 38 | (19.2) | 29 | (17.7) | 9 | (26.5) |
| 51-75% | 32 | (16.2) | 23 | (14.0) | 9 | (26.5) |
| >75% | 35 | (17.7) | 25 | (15.2) | 10 | (29.4) |

** Unable to retrieve the chest radiographs of two patients*

**Table 4.** Antibiotic utilization among patients admitted with COVID-19 infection admitted in UP-PGH

| Antibiotics, No. (%) | Overall (N=200) | | Illness severity on admission | | | |
|---|---|---|---|---|---|---|
| | | | Mild (N=41) | Moderate (N=99) | Severe (N=32) | Critical (N=28) |
| Macrolide | 96 | (48.0) | 6 | 54 | 18 | 18 |
| Penicillin | 88 | (44.0) | 2 | 37 | 26 | 23 |
| Cephalosporin | 72 | (36.0) | 4 | 41 | 16 | 11 |
| Carbapenem | 29 | (14.5) | 0 | 9 | 6 | 14 |
| Quinolone | 13 | (6.5) | 0 | 7 | 1 | 5 |
| Polymixin | 10 | (5.0) | 0 | 2 | 0 | 8 |
| Vancomycin | 7 | (3.5) | 0 | 2 | 2 | 3 |
| Aminoglycoside | 6 | (3.0) | 0 | 0 | 2 | 4 |
| Tetracycline | 5 | (2.5) | 0 | 1 | 0 | 4 |
| Clindamycin | 3 | (1.5) | 0 | 1 | 0 | 2 |
| Metronidazole | 3 | (1.5) | 0 | 1 | 1 | 1 |
| Linezolid | 2 | (1.0) | 0 | 0 | 0 | 2 |
| Trimethoprim-sulfamethoxazole | 2 | (1.0) | 0 | 0 | 1 | 1 |
| Fosfomycin / Nitrofurantoin | 2 | (1.0) | 1 | 1 | 0 | 0 |
| Antituberculous drugs | 9 | (4.5) | 0 | 5 | 2 | 2 |
| Antifungal | 5 | (2.5) | 0 | 1 | 2 | 2 |

hemoperfusion were likewise given as adjunctive therapy. The use of investigational agents is summarized in Table 5.

In this early stage of the pandemic, corticosteroids (n=15) were given for other indications such as COPD, septic shock, and hematologic malignancies. Eight of the patients given corticosteroids survived, while seven died. Dexamethasone was not yet part of the standard of care for COVID-19 patients with severe disease during this time.

## Community-Acquired Co-infection

Twenty-two (11%) patients had concomitant bacterial co-infection. Two were isolated from the blood of patients with severe and critical diseases. Pulmonary bacterial co-infection was documented in 20 patients - six with mild, 10 moderate, three severe, and one critical condition.

Twenty-six organisms were from respiratory specimens, with six patients having multiple bacterial isolates. The

**Table 5.** Use of Investigational therapies among patients with COVID-19 admitted in UP-PGH

| Investigational Therapy | Overall (N=200) | | Illness severity on admission | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mild (N=41) | | Moderate (N=99) | | Severe (N=32) | | Critical (N=28) | |
| ***Any use, No. (%)*** | | | | | | | | | | |
| Hydroxychloroquine or Chloroquine | 78 | (39.0) | 0 | (0) | 38 | (38.4) | 25 | (78.1) | 15 | (53.6) |
| Lopinavir/ritonavir | 16 | (8.0) | 1 | (2.4) | 5 | (5.1) | 4 | (12.5) | 6 | (21.4) |
| Tocilizumab | 24 | (12.0) | 0 | (0) | 2 | (2.0) | 7 | (21.9) | 15 | (53.6) |
| ***Monotherapy, No. (%)*** | | | | | | | | | | |
| Hydroxychloroquine or Chloroquine | 54 | (27.0) | 0 | (0) | 35 | (35.4) | 16 | (50.0) | 3 | (10.7) |
| Lopinavir/ritonavir | 7 | (3.5) | 1 | (2.4) | 4 | (4.0) | 1 | (3.1) | 1 | (3.6) |
| Tocilizumab | 2 | (1.0) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (7.1) |
| ***Combination, No. (%)*** | | | | | | | | | | |
| HCQ/CQ + LPV/R | 4 | (2.0) | 0 | (0) | 1 | (1.0) | 2 | (6.3) | 1 | (3.6) |
| HCQ/CQ + Tocilizumab | 17 | (8.5) | 0 | (0) | 2 | (2.0) | 6 | (18.8) | 9 | (32.1) |
| LPV/R + Tocilizumab | 2 | (1.0) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (7.1) |
| HCQ/CQ + LPV/R + Tocilizumab | 3 | (1.5) | 0 | (0) | 0 | (0) | 1 | (3.1) | 2 | (7.1) |
| ***Other interventions, No. (%)*** | | | | | | | | | | |
| Oseltamivir | 13 | (6.5) | 0 | (0) | 5 | (5.1) | 6 | (18.8) | 2 | (7.1) |
| Corticosteroid | 15 | (7.5) | 0 | (0) | 6 | (6.1) | 3 | (9.4) | 6 | (21.4) |
| Convalescent plasma | 7 | (3.5) | 0 | (0) | 1 | (1.0) | 1 | (3.1) | 5 | (17.9) |
| Hemoperfusion | 6 | (3.0) | 0 | (0) | 0 | (0) | 1 | (3.1) | 5 | (17.9) |

most common organism isolated from respiratory samples was *Klebsiella pneumoniae* (n=17), followed by *Staphylococcus aureus* (n=4), *Citrobacter koseri* (n=2), *Acinetobacter baumannii* (n=2), and *Pseudomonas aeruginosa* (n=1). Most of the organisms isolated were susceptible to antibiotics except for four isolates of extended-spectrum beta-lactamase (ESBL)-producing *K. pneumoniae* and three isolates of methicillin-resistant *S. aureus* (MRSA). The two organisms isolated from the blood were *A. baumannii* and ESBL-producing *Escherichia coli.*

Pulmonary viral co-infection with Influenza B was documented in only one patient with severe disease. Multiplex nucleic acid tests for respiratory pathogens are not available at the UP-PGH, and the patient's test was done at another hospital. Notably, two patients also had concurrent herpes zoster at the time of admission.

## Clinical Events and In-hospital Mortality

Overall 52.0% (n=104) subsequently required oxygen supplementation, of whom 13.5% (14/104) required high flow oxygen, 36.5% (38/104) required ventilatory support, and 66.3% (n=69/104) developed ARDS. Of the cohort, 29.0% (n=58) needed ICU admission, 17.5% (n=35) developed acute kidney injury, 9.5% (n=19) needed renal replacement therapy, 4.5% (n=9) had acute stroke, 2.0% (n=4) had acute myocardial infarction, 36.0% (n=72) had sepsis and septic shock, and 16.0% (n=32) had healthcare-associated infection. Of the latter, 16.0% (n=33) had healthcare-associated pneumonia, 0.5% (n=1) had CRBSI, and 0.5% (n=1) had CAUTI.

The in-hospital mortality rate was 17.5% (35/200). Mortality rates were 0% for mild, (7/99) 7.1% for moderate, (8/32) 25% for severe, and (20/28) 71.4% for critical COVID-19 cases. Of the seven patients with moderate disease and died, 6 had disease progression, while one succumbed to massive gastrointestinal bleeding.

Among those who died, the most common cause of death was ARDS from COVID-19 pneumonia (n=10), followed by nosocomial pneumonia (n=9), sepsis and septic shock (n=8), acute coronary syndrome (n=3), acute stroke (n=2), gastrointestinal bleeding (n=2), and pneumothorax (n=1).

## Factors associated with mortality

ICU admission [34 (97.2%) vs. 24 (14.6%), p<0.001] and invasive ventilation [33 (94.3%) vs. 5 (3.0%), p<0.001] were both significantly associated with non-survival. Other clinical events associated with non-survival were the development of ARDS [29 (82.9%) vs. 40 (24.2%), p<0.001], acute kidney injury [23 (65.7%) vs. 12 (7.3%), p<0.001], need for hemodialysis [10 (28.6%) vs. 9 (5.4%), p<0.001], sepsis [31 (88.6%) vs. 41 (24.9%), p<0.001], septic shock [23 (65.7%) vs. 4 (2.4%), p<0.001], nosocomial infection [18 (51.4%) vs 14 (8.5%), p<0.001], nosocomial pneumonia [18 (51.4%) vs. 14 (8.5%), p<0.001], acute stroke [6 (17.1%) vs. 3 (1.82%), p<0.001], and acute myocardial infarction [3 (8.6%) vs. 1 (0.6%), p=0.002].

Non-survivors spent a median of 7 (IQR 3 to 12) days in the hospital compared to 26 (IQR 16 to 38) days for survivors (p<0.001).

# DISCUSSION

Our retrospective cohort validates existing published information regarding characteristics of patients with COVID-19: most affected patients are older with a slight male predominance, and comorbidities such as hypertension or DM are often present.[6-8] The clinical presentation on admission is also similar to what has already been

described, with cough, fever, and shortness of breath being most prominent.[6]

Many of the patients had radiographic abnormalities at baseline, similar to other studies.[9-11] However, because of the varied population strata, coexisting illnesses, and the patients brought to UP-PGH, we could not make conclusions regarding early x-ray findings predictive for COVID-19. Nonetheless, the x-ray findings among patients with COVID pneumonia tend to involve the lung diffusely, i.e., involving the bilateral lungs, spanning the upper to lower lobes and central to peripheral lung zones, again consistent with published data.[6] The most common chest x-ray finding of ground glass pulmonary opacities is also consistent with earlier studies from Korea and China.[9,12] Consolidation is seen in a little more than half of the patients, while fibrotic densities were rarely seen as it is usually a hallmark of past infection or inflammation.[13] While many patients who had no discernible lung opacities at baseline survived, two such patients died. Thus, a normal baseline x-ray in a patient with COVID-19 infection does not predict outcome and may invoke the need to do further imaging. A chest x-ray should not be used as the sole basis to diagnose COVID-19.

Despite similarities with previously published studies among COVID-19 patients, our cohort offers other insights unique to our patient population. First, a large proportion of our patients (41%) required oxygen upon admission. Second, more patients with underlying neurologic disease, particularly a history of ischemic stroke, did not survive. Third, bacterial co-infection (11%) is higher in our cohort compared to published reports. And finally, *K. pneumoniae* was the most common community-acquired pathogen isolated in our cohort, which differs from previously reported co-pathogens of SARS-CoV-2.[14-16]

Almost half of our patients (41%) required oxygen upon admission. This likely reflects the patient population seen at the UP-PGH, a tertiary level hospital and often the referral hospital of choice for sicker patients. Not surprisingly, we found that the patients who presented with respiratory distress upon admission manifested by higher respiratory rates and lower oxygen saturation at baseline were less likely to survive. That Those patients ended when they were more symptomatic may also reflect a delay in their consultation. The median duration from symptom onset to hospital admission was ten days (IQR 6 to 14). This delayed presentation is also not unexpected. Historically, patients are seen in the UP-PGH present later in their disease because of multiple factors, including financial constraints and difficulty accessing healthcare. The shorter hospital stay for non-survivors reflects the fact that non-survivors died early during their hospital stay.

In our cohort, the presence of neurologic disease, particularly a history of stroke, was more common among non-survivors than survivors. Findings from published studies vary. A study that utilized a global COVID-19 database (TriNetX) found no association between the history of stroke and in-hospital mortality among 891 stroke cases vs. 32,136 controls.[17] They concluded that older age and several comorbid illnesses among these patients make them vulnerable to worse outcomes. However, a retrospective multicenter cohort study of 3,248 patients in the US (387 with a history of stroke) found a significant association of stroke history to in-hospital mortality after adjusting for all comorbidities (adjusted odds ratio, 1.28 [95% CI, 1.01–1.63].[18] Similarly, a retrospective cohort study of 1875 patients in China, of whom 50 had a prior history of stroke, showed that after propensity-matched analysis, a more significant proportion of patients with stroke history were admitted to the ICU requiring ventilation and were likely to die.[19] Differences in research methodologies and limitations in each of the strategies employed could have contributed to different results. Whether this is a common phenomenon or could have been affected by the racial difference, needs to be explored. This should be investigated further using larger sample size and employing multivariable analysis.

Bacterial co-infection (11%) was higher in our cohort compared to current published data. A meta-analysis which included data from different countries (N=3,338) revealed that bacterial co-infection was identified in only 3.5% (95% CI 0.4% - 6.7%) of COVID-19 patients.[14] In the Netherlands, bacterial co-infection ranged from 2.8% (3/107) to 8% (8/100).[16,20] Likewise, a large cohort of patients in Spain reported low community-acquired co-infection at 3.1% (31/989).[15] We hypothesize that our higher rate of culture-based co-infection may be because of the following: (1) limited access to antibiotics in the underserved communities because of the enhanced community quarantine, and (2) use of a hospital clinical pathway which standardized early collection of blood and respiratory specimens for microbiologic evaluation from all patients suspected of COVID-19 infection before administration of antibiotics.

The finding of *K. pneumoniae* as the most common underlying respiratory pathogen is unique to our cohort. Other studies have reported bacterial co-pathogens, including *Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella, Haemophilus influenzae, P. aeruginosa, Streptococcus pneumoniae,* and *S. aureus.*[14-16] This finding is not surprising in South-east Asia, where gram-negative pathogens are considered important causes of community-acquired pneumonia.[21] The 2019 Antimicrobial Resistance Surveillance Project (ARSP) reported *K. pneumoniae* as the most commonly isolated respiratory pathogen in the Philippines.[22] In that report, 54.2% (n=8,290) of *K. pneumoniae* isolates were from respiratory specimens, of which 49.9% (n=7,632) were community-acquired.

Many (61%) of our patients received empiric antimicrobials on admission, with antibiotics more frequently given for a more severe disease. The use of antimicrobials is not uncommon for COVID-19, and up to 72% of patients are often given antibiotics despite low rates of bacterial co-infection.[23] The impulse to start antibiotics up front may

have been driven by studies on patients with influenza, which show co-infection rates ranging from 2-65% based on a meta-analysis.[24] The finding of higher bacterial co-infection in our cohort should be considered as it may warrant empiric antibacterial coverage for *K. pneumoniae*. Fortunately, most of the bacteria isolated from our patients did not exhibit antimicrobial resistance. Thus, following the empiric antibiotic recommendations of the Philippine Community-Acquired Pneumonia Clinical Practice Guidelines is warranted.[25]

In our cohort, non-survivors were more likely to develop complications including ARDS, AKI requiring RRT, sepsis and septic shock, nosocomial infections including pneumonia, acute stroke, and acute myocardial infection. These findings are not novel and are consistent with other published studies. For example, a study of 2,529 patients with COVID-19 in China showed that coronary heart disease was an independent risk factor for mortality.[26] Another study of 1,461 patients with COVID-19 in the United States also identified abnormal respiratory parameters on admission, and initial laboratory results showing renal insufficiency and liver injury as factors associated with in-hospital mortality.[27]

In addition to identifying factors associated with mortality, a few studies have also developed scoring systems to predict COVID-19 mortality.[26,28-30.] One created a three-tiered risk score based on only two variables, age and CRP thresholds.[28] Another identified comorbidities, age, lymphocyte count, and LDH as predictors of mortality.[29] In another, old age, heart disease, lymphocyte %, procalcitonin, and D-dimer were independently related to mortality.[26] In contrast, a US-based study used more variables and validated the model internally using independent datasets.[30] We were unable to create a similar scoring system given the limited number of patients in this study. Still, the creation of one relevant to our setting and using a more extensive database is underway.

A high rate of use of HCQ/CQ was observed, reflecting that the individuals included in this study were admitted during the early part of the pandemic. The use of tocilizumab was limited because of the drug's scarcity during the pandemic's early period

Overall mortality in our cohort was 17.5%. This is similar to other studies during the pandemic's early period, with a mortality rate ranging from 4.3%-21%.[31-33] Locally, reported mortality rates were 15% (6/40) in a private tertiary hospital and 21.4% (9/42) in a public tertiary COVID-19 referral center similar to ours.[34,35] This high mortality rate is likely indicative of the many unknowns during this period of the pandemic when treatment regimens were all experimental and being studied under clinical trials, when healthcare providers were still gaining knowledge and experience on the optimal management for COVID-19 patients, and when cases and hospitalization initially peaked. A decline in mortality rate was observed in the US in the first six months of the pandemic when COVID-19 cases in the surrounding communities were also lower.[36]

## CONCLUSION

Our study confirms that patients hospitalized with COVID-19 are more likely to be older and have underlying comorbid conditions. Like in other studies, empiric antimicrobials were prescribed for many patients, with 61% of our study cohort receiving empiric antibiotics. The bacterial co-infection rate was slightly higher in our cohort, with *K. pneumoniae* as the predominant co-pathogen. However, most of the bacterial isolates were susceptible to broad-spectrum antibiotics, emphasizing the need to de-escalate their use based on local community-acquired pneumonia guidelines. The mortality rate was 17.5% during this early period of the pandemic, though this is comparable with other institutions. We confirmed factors associated with mortality previously recognized in other studies, including ICU admission or invasive ventilation and development of complications such as ARDS, AKI requiring RRT, septic shock, stroke, and cardiovascular events.

### Statement of Authorship

All authors participated in the data collection and analysis and approved the final version submitted.

### Author Disclosure

All authors declared no conflicts of interest.

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