International Journal of Multidisciplinary Research and Growth Evaluation.

Mortality Risk Factors in Severe and Critical COVID-19 Patients at Antsiranana University Hospital

Filamant Tombolaza Canut [1*], Raherinirina Angelo Fulgence [2], Totohasina André [3]
[1] Thematic Doctoral School Science, Culture, Society, and Development at the University of Toamasina, Toamasina, Madagascar
[2] Research Center for the Teaching of Mathematics, University of Fianarantsoa, Fianarantsoa, Madagascar
[3] Department of Mathematics and Informatics, University of Antsiranana, Antsiranana, Madagascar

* Corresponding Author: **Filamant Tombolaza Canut**

Article Info

ISSN (online): 2582-7138
Volume: 05
Issue: 06
November-December 2024
Received: 05-09-2024
Accepted: 07-10-2024
Page No: 377-388

Abstract
Backgrounds: This study focuses on identifying risk factors associated with mortality in patients with severe or critical COVID- 19 at the University Hospital of Antsiranana, Madagascar. Since the pandemic's onset, African healthcare systems have faced significant challenges due to limited intensive care resources, contributing to higher mortality rates. Madagascar has reported a COVID-19 case fatality rate of around 2%. The aim of this study is to identify mortal- ity risk factors to improve patient management and reduce death rates in severely ill patients.
Methods: This retrospective cohort study was conducted from March 2020 to March 2022, including hospitalized patients with confirmed or probable COVID-19 infection. Data on demographics, clinical symptoms, laboratory tests, and treatments were collected. Univariate and multivariate analyses were performed to identify risk factors associated with mortality.
Results: Out of 124 patients, 25 (20.2%) died. The median age was 58.6 years, with 48.4% over the age of 60. The most common symptoms were cough (73.4%), dyspnea (70.2%), and fever (68.5%). Comorbidities were present in 65.32% of the patients, with hypertension (50%) and diabetes (29.8%) being the most frequent. Multivariate anal- ysis revealed that cardiac and respiratory deterioration, as well as shock, were strongly associated with increased mortality risk
Conclusion: The findings confirm that comorbidities, particularly hypertension and diabetes, are significant risk factors for COVID-19 mortality. Respiratory decline, cardiac decompensation, and altered consciousness at admis- sion were also critical prognostic indicators. Hospital mortality rates were consistent with other studies in similar low-resource settings, though the actual rates may be underreported due to limited healthcare resources.
This study highlights the importance of early management of comorbidities and respiratory and cardiac complications in severe COVID-19 patients to reduce mortality.

DOI: https://doi.org/10.54660/.IJMRGE.2024.5.6.377-388

Keywords: COVID-19, hospitalization, severe form, mortality risk

1. Introduction

Since the first case of COVID-19 was reported in Wuhan, China, in December 2019, the disease has developed into a global pandemic affecting nearly every country [1]. By December 14, 2021, over 268 million cases and approximately 5.3 million deaths had been documented worldwide. While the pandemic's impact in Africa has been less severe compared to other regions, the overall consequences are still significant, particularly due to the vulnerability of health systems [2]. COVID-19 mortality rates in Africa range from 0.1% to 8.8%, with a notably harsher second wave [3]. Several factors, including underreporting of deaths, lack of testing, potential cross- immunity, and the youthful demographic structure, may account for the relatively low mortality rates [4].

A recent observational study across 64 hospitals in 10 African countries reported a 30-day hospital mortality rate of 48.2% among patients admitted to intensive care units, highlighting resource scarcity as a critical factor in excess mortality [5].
In Madagascar, where intensive care resources are limited, severely ill patients often receive care in general wards, a situation exacerbated during the COVID-19 outbreak. Since the first confirmed case in March 2020 [6], Madagascar has reported 53,412 confirmed cases and 1,117 deaths, with a fatality rate of around 2% (Ministry of Public Health, 01/08/2022). This study aims to identify the risk factors associated with mortality in patients hospi- talized with severe or critical COVID-19, ultimately contributing to improved management and reduced mortality rates.

2. Materials and Methods

The study was conducted at the Tanambao Antsiranana University Hospital Center

2.1. Study type

This was a retrospective cohort study.

2.2. Study period

The study population consisted of patients hospitalized for COVID-19

2.3. Study population

The study covered 2 years, from March 2020 to March 2022.

2.4. Inclusion criteria

Inclusion criteria included patients who: had confirmed COVID-19 via RT-PCR or GeneXpert, had probable COVID-19 based on clinical signs and compatible imaging or positive serology, were hospitalized during the study period

2.5. Exclusion criteria

Exclusion criteria included: Asymptomatic cases, hospital admissions solely for isolation without clinical indi- cations, unknown discharge status, incomplete medical records that precluded essential data collection, discharges against medical advice or patient escape, transfers to others facilities with unknown patient outcomes.

2.6. Studied Variables

Demographic Data: Age, gender, admission and discharge dates, clinical and paraclinical data: symptoms, comorbidities (known before and discovered during hospitalization), clinical signs at admission, initial laboratory results, imaging results, ECG interpretations, and complications occurring during hospitalization, .management: treatments received prior to and during hospitalization, including both pharmacological and non- pharmacological interventions,

2.7. Data collection and analysis Data

Data were collected on paper forms and then entered into a database using Epi Info 7.2.2.

2.8. Statistical analysis

Quantitative variables were summarized using medians and interquartile ranges. Univariate comparisons be- tween survivors and deceased patients were performed using Chi-square tests or Fisher's exact tests for qualitative variables and Mann-Whitney tests for quantitative variables. Imaging and ECG data were not included in univariate analysis to avoid selection bias. A multivariate analysis using multiple binary logistic regression identified factors associated with mortality. A p-value $< 0.05$was considered significant, with a 95% confidence interval. Statistical analysis was performed using R and Stata 17.

3. Results

During the study, we had 205 hospitalized patients, of whom 81 were excluded from our study, leaving 124 patients retained, including 99 (79,83%) survivors and 25 (20,17%) deceased.

3.1. Demographic Characteristics of Patients

The study included a total of 124 patients, with a median age of 58.6 years (IQR: 46.3-67.2). The age peak was observed in the 60-69 year range, accounting for 30.6% of the sample. Notably, 48.4% of the patients were over 60 years old. Among the participants, 59.7% were male and 40.3% were female, resulting in a sex ratio of 1.48.

3.2. Clinical characteristics of patients at anamnesis

The most frequently reported symptoms among patients were cough (73.4%), dyspnea (70.2%), and fever (68.5%). This suggests that respiratory and systemic manifestations were predominant in this patient population, highlighting the need for careful monitoring and management of these symptoms during treatment.

Table 1: Initial symptoms

Symptoms	n	%
Cough	91	73.4
Dyspnea	87	70.2
Fever	85	68.5
Fatigue	72	58.1
Arthralgia/Myalgia	70	56.5
Headache	51	41.1
Sputum	28	22.6
Chest Pain	26	21.0
Diarrhea	20	16.1
Rhinorrhea	16	12.9
Altered Consciousness	10	8.1
Vomiting	10	8.1
Anosmia	9	7.3
Ageusia	6	4.8
Dizziness	4	3.2
Sore Throat	3	2.4
Hiccups	2	1.6
Abdominal Pain	2	1.6
Ear Pain	1	0.8
Neurological Deficit	1	0.8

3.3. Medical Hostory

The results indicates that a significant proportion of patients received azithromycin and other antibiotics (over 30%), highlighting a proactive approach to treating potential bacterial infections before hospitalization. Addition- ally, the use of corticosteroids (29%) suggests a focus on managing inflammation in patients, which is crucial in respiratory conditions.

Table 2: Treatments Received Before Hospitalization of Patients

Treatments	n	%
Azithromycin	38	30.8
Antibiotics	37	29.8
Corticosteroids	36	29.0
Anticoagulation	24	19.4
Oxygen Therapy	14	11.3
Hydroxychloroquine	10	8.1
ACE Inhibitors/ARBs	6	4.8
Aspirin	6	4.8
Antimalarials	5	4.0
Statins	3	2.4
Diuretics	2	1.6
Clopidogrel	1	0.8
Colchicine	1	0.8

3.4. Patient comorbidities

Among the 124 patients included, 81 (65.32%) had one or more comorbidities. The results indicates that hypertension was the most prevalent comorbidity among patients, affecting 50% of them, followed by diabetes mellitus at 29.8% and obesity at 21%.

Table 3: Known Comorbidities before Admission

Variables	n	%
Hypertension	62	50.0
Diabetes Mellitus	37	29.8
Obesity	26	21.0
Cardiopathy	4	3.2
Coronary Artery Disease	2	1.6
COPD	1	0.8
Asthma	3	2.4
Chronic Respiratory Disease	1	0.8
Tuberculosis	2	1.6
Cerebrovascular Disease	2	1.6
Chronic Neurological Disease	1	0.8
Chronic Kidney Disease	2	1.6
Cancer	1	0.8

The table 4 reveals that among the newly discovered comorbidities at admission, diabetes mellitus is the most common, affecting 12.1% of patients, while hypertension and cardiopathy are present in only 1.6% and 0.8% of patients, respectively.

Table 4: Newly Discovered Comorbidities at Admission

Variables	n	%
Hypertension	2	1.6
Diabetes Mellitus	15	12.1
Cardiopathy	1	0.8

The table 5 indicates that azithromycin, antibiotics, and corticosteroids are the most commonly prescribed long-term treatments, each accounting for around 30% of the patients.

Table 5: Long-Term Treatment of Patients

Treatments	N	%
Azithromycin	38	30.8
Antibiotics	37	29.8
Corticosteroids	36	29.0
Anticoagulation	24	19.4
Oxygen Therapy	14	11.3
Hydroxychloroquine	10	8.1
ACE Inhibitors/ARBs	6	4.8
Aspirin	6	4.8
Antimalarials	5	4.0
Statins	3	2.4
Diuretics	2	1.6
Clopidogrel	1	0.8
Colchicine	1	0.8

3.4. Vital signs at admission

Table 6 presents the vital signs of patients at admission, highlighting key parameters that provide insight into their initial clinical status.

Table 6: Vital signs at admission

Vital Parameters	Median (IQR)
Systolic Blood Pressure (mmHg)	125 (110-140)
Diastolic Blood Pressure (mmHg)	80 (70-90)
Temperature (°C)	37.1 (36.6-38.2)
Heart Rate (bpm)	92 (85-104)
Respiratory Rate (cpm)	26 (23-30)
SpO2 % in Ambient Air	88 (82-91)

3.5. Physical Signs at Admission

At admission, pneumonia was the most prevalent physical sign, affecting 61.3% of patients, indicating a significant respiratory burden among the cohort. Additionally, the qSOFA scores revealed a concerning number of patients with moderate to high risk of sepsis, as 68.5% scored 2 points or higher, suggesting critical clinical conditions that require immediate attention.

Table 7: Physical Signs at Admission

Physical Signs	n	%
Pneumonia	76	61.3
Respiratory Distress	23	18.5
Heart Failure Decompensation	17	13.7
Altered Consciousness (Glasgow < 15)	10	8.1
Neurological Deficits	3	2.4

At admission, the distribution of qSOFA scores was as follows: 0 points in 1 patient (0.8%), 1 point in 25 patients (20.2%), 2 points in 85 patients (68.5%), and 3 points in 13 patients (10.5%).

3.6. Initial Biological Tests

The initial biological tests indicate that the cohort had a median hemoglobin level of 14.4 g/dL, which falls within a normal range, suggesting adequate oxygen-carrying capacity. However, the elevated C-reactive protein (CRP) level at 48 mg/L and the high median D-dimer level of 782 ng/ml point to significant inflammation and potential clotting issues, raising concerns about the presence of underlying infections or thromboembolic even

Table 8: Initial Biological Tests

Initial Biological Tests	Median (IQR)
Hemoglobin in g/dL	14.4 (13.1-15.9)
White Blood Cells in G/L	9.85 (7-15.4)
Neutrophils in G/L	7.4 (4.9-12)
Lymphocytes in G/L	1.3 (0.8-2)
Platelets in G/L	293 (220-403)
CRP in mg/L	48 (12-114)
Creatinine in µmol/L	98 (78-121)
Urea in mmol/L	6.9 (5-10)
Glucose in mmol/L	7.95 (6.1-13.5)
D-dimers in ng/ml	782 (441-1784)

3.7. Scanning Lesions in Patients

The results of chest scans show that 62.3% of patients had lesions, with ground-glass opacities being the most common, observed in 59.7% of patients. The majority of lesions were bilateral, and the classification reveals that 41.6% of patients had pulmonary involvement between 50 and 75%, indicating a potential severity of the respiratory conditions.

Table 9: Scanning Lesions in Patients

Observed Lesions	n	%
Patients who underwent chest CT	77	62.3
Normal chest CT	12	15.6
Location of lesions		
- Peripheral	27	34.2
- Subpleural	22	28.6
- Basal	14	18.2
- Apical	1	1.3
Bilateral involvement	41	53.2
Median percentage of pulmonary involvement	50	(IQR: 5-95)
Classification of lesions		
- Involvement < 25%	6	7.8
- Involvement 25-50%	21	27.3
- Involvement 50-75%	32	41.6

The characteristics of lesions observed in chest scans, with ground-glass opacities being the most common, found in 59.7% of patients, followed by reticular opacities in 25.8% and consolidations in 24.2%. Other findings included pleural effusions in 8.1%, emphysema in 5.6%, crazy paving in 4.8%, atelectasis in 1.6%, bronchograms in 1.6%, and pulmonary embolism in 0.8%.

3.8. ECG Tracings

The ECG findings indicate that T-wave abnormalities were the most common electrical abnormality, observed in 22.6% of patients, while a significant proportion of patients exhibited normal ECG readings as well. Other notable abnormalities included tachycardia and various arrhythmias, highlighting the diverse cardiac issues present in this cohort. The ECG electrical abnormalities observed among patients are as follows: T-wave abnormality was found in 28 patients, accounting for 22.6% of the sample. Normal ECG tracings were noted in 27 patients (22.3%). Tachycardia was observed in 10 patients (8.3%), while supraventricular arrhythmia affected 7 patients (5.8%). Left ventricular hypertrophy was identified in 5 patients (4.2%), and right ventricular hypertrophy in 4 patients (3.3%). ST-segment abnormality, ventricular arrhythmia, and bradycardia were each found in 4 patients (3.3% and 2.5%, respectively). Finally, left atrial enlargement, the S1Q3 pattern, and right atrial enlargement were each seen in 1 patient, representing 0.8% of the sample

3.9. Complications Occurring During Hospitalization

During hospitalization, complications were reported in 80.6% of patients, with respiratory deterioration and diabetes decompensation being the most common, both occurring within a median duration of approximately 3 to 3.5 days after admission.

The complications that occurred during hospitalization were as follows: A total of 100 patients (80.6%) experienced complications. Respiratory deterioration was observed in 40 patients (32.3%), with a median onset of 3.5 days (IQR: 3-6 days). Heart decompensation occurred in 13 patients (10.5%) after a median of 3 days (IQR: 2-7 days). Acute coronary syndrome and cardiac arrhythmia were each noted in 2 patients (1.6%), with a median onset of 6 days (IQR: 2-10.5) and 4.5 days (IQR: 1.5-8.5), respectively. Diabetes decompensation affected 36 patients (29.0%) with a median onset of 3 days (IQR: 2-6), and diabetic ketoacidosis was seen

in 10 patients (8.1%) after 3 days (IQR: 2-6). Renal failure occurred in 10 patients (8.1%) with a median onset of 6.5 days (IQR: 3-10). Gastrointestinal bleeding was observed in 8 patients (6.5%) with a median onset of 9 days (IQR: 6-11). Shock affected 10 patients (8.1%) after a median of 12 days (IQR: 10-18). Infection was noted in 9 patients (7.3%) with a median onset of 9 days (IQR: 5-17). Altered consciousness occurred in 10 patients (8.1%) with a median onset of 5 days (IQR: 3-12). Seizures were observed in 1 patient (0.8%) with a median onset of 3 days (IQR: 2-4), and agitation occurred in 4 patients (3.2%) with a median onset of 9.5 days (IQR: 3-15)

3.10. Patients outcomes

Among the total of 124 patients, 99 (79.8%) survived while 25 (20.2%) did not. The median duration of hospitalization was 12 days (IQR: 0-84).

When examining the average length of stay based on SpO2 levels, patients with SpO2 greater than 94% had an average stay of 12.8 days, those with SpO2 less than 94% and requiring 6-10 liters per minute of oxygen had an average stay of 15.7 days, and patients with SpO2 less than 94% and requiring more than 10 liters per minute had an average stay of 18.5 days.

3.11. Univariate Analysis

A comparison of demographic data, clinical characteristics of patients, and laboratory results was conducted between survivors and non-survivors

Table 10: Comparison of Patient Demographoc Characteristics Between Survivors and Deceased Patientes

Variable	Total n (%)	Survivors n (%)	Deceased n (%)	p-value
Age (Median, IQR) in year	58,6 (46,3-67,2)	58,7 (45,9-66,4)	58,2 (48,3-68,2)	0,528
<30	2 (1,6)	2 (2,0)	0 (0)	
30-39	10 (8,1)	9 (9,1)	1 (4,0)	
40-49	22 (17,7)	19 (19,2)	3 (12,0)	0,938
50-59	30 (24,2)	24 (24,2)	6 (24,0)	
60-69	38 (30,6)	32 (32,3)	6 (24,0)	
≥70	22 (17,7)	17 (17,2)	5 (20,0)	
Male	74 (59,7)	58 (58,6)	16 (64,0)	0,114

There was no statistically significant difference between the two patient groups regarding age.

Table 11: Comparison of initial symptoms Between Deceased Patients and Survivors and Their time to Progression

Symptoms	Total n (%)	Survivors n (%)	Deceased n (%)	p-value
Fever	85 (68,5)	71 (71,7)	14 (56,0)	0,145
Cough	91 (73,4)	76 (76,8)	15 (60,0)	0,097
Sputum	28 (22,6)	24 (24,2)	4 (16,0)	0,397
dyspnea	87 (70,2)	70 (70,7)	18 (72,0)	0,886
Hemoptysis	2 (1,6)	2 (2,0)	0 (0)	
Chest pain	27 (21,8)	23 (23,2)	4 (20,0)	0,743
Arthralgia/Myalgia	**70 (56,5)**	**61 (61,6)**	**9 (36,0)**	**0,030**
Fatigue	72 (58,1)	59 (59,6)	13 (48,0)	0,305
Rhinorrhea	18 (14,5)	15 (15,2)	3 (12,0)	0,686
Headache	**51 (41,1)**	**46 (46,5)**	**5 (24,0)**	**0,043**
Sore throat	3 (2,4)	3 (3,0)	0 (0)	
Diarrhea	22 (17,7)	18 (18,2)	4 (16,0)	0,799
Abdominal pain	1 (0,8)	1 (1,0)	0 (0)	
Vomiting	10 (8,1)	7 (7,1)	3 (8,0)	0,856
Other gastrointestinal disorders	10 (8,1)	7 (7,1)	2 (8,0)	0,856

Arthralgia/myalgia and headache were statistically more frequent among survivors. There was no significant difference for other symptoms

Table 12: Comparison of initial symptoms between deceased and surviving patients (continued)

Symptoms	Total n (%)	Survivors n (%)	Deceased n (%)	p-value
Hiccups	2 (1.6)	2 (2.0)	0 (0)	-
Ageusia	6 (4.8)	5 (5.1)	1 (4.0)	0.783
Anosmia	9 (7.3)	8 (8.1)	1 (4.0)	0.493
Altered consciousness	**17 (13.7)**	**6 (6.1)**	**11 (44.0)**	**<0.001**
Seizures	2 (1.6)	1 (1.0)	1 (4.0)	0.290
Neurological deficit	1 (0.8)	1 (1.0)	0 (0)	-
Dizziness	4 (3.2)	4 (4.0)	0 (0)	0.342
Nasal congestion	1 (0.8)	0 (0)	1 (4.0)	0.177
Median (IQR)	8 (6-13)	9 (6-13)	7 (6-13)	0.274
< 8 days	52 (41.9)	41 (41.4)	11 (44.0)	0.800
8 – 14 days	45 (36.3)	37 (37.4)	8 (32.0)	0.640
≥ 15 days	27 (21.8)	21 (21.2)	6 (24.0)	0.770

The alteration of consciousness was the most frequently encountered and statistically significant

Table 13: Comparison of treatments received between survivors and deceased patients

Variable	Total n (%)	Survivors n (%)	Deceased n (%)	p-value
Previous care in another facility	67 (54.0)	52 (52.5)	15 (60.0)	0.489
Previous care (outside the hospital)	52 (41.9)	39 (39.4)	13 (52.0)	0.219
▪ Public hospital	4 (7.7)	3 (7.7)	1 (7.7)	1.000
▪ Private hospital	7 (13.5)	5 (12.8)	2 (15.4)	0.781
▪ Field hospital	9 (17.3)	6 (15.4)	3 (23.1)	0.476
▪ Home care	20(38.5)	17 (43.6)	3 (23.1)	0.127
▪ Emergency unit	2 (3.8)	2 (5.1)	0 (0)	1.000
▪ Conventional hospitalization	3 (5.8)	3 (7.7)	0 (0)	0.565
Number of days in another facility	5 (3-6)	5 (3-6)	5 (3-7)	0.423
Previous care in another facility	67 (54.0)	52 (52.5)	15 (60.0)	0.489
Previous care (outside the hospital)	52 (41.9)	39 (39.4)	13 (52.0)	0.219

The Table 13 reveals treatment received prior to hospitalization shows no significant differences between survivors and deceased patients, suggesting that previous care may not be a critical factor in determining outcomes.

Table 14: Comparison of known comorbidities prior to admission between survivors and deceased patients

Variable	Total n (%)	Survivors n (%)	Deceased n (%)	p-value
Known comorbidities at admission	**93 (75.0)**	**71 (71.7)**	**22 (88.0)**	**0.018**
Number of known comorbidities (median, IQR)	**1 (1-2)**	**1 (0-2)**	**2 (1-3)**	**0.001**
▪ Hypertension	61 (49.2)	48 (48.5)	13 (52.0)	0.321
▪ Diabetes	36 (29.0)	27 (27.3)	9 (36.0)	0.057
▪ Obesity/Overweight	25 (20.2)	22 (22.2)	3 (12.0)	0.342
▪ Cardiopathy	4 (3.2)	3 (3.0)	1 (4.0)	0.389
▪ Coronary artery disease	2 (1.6)	1 (1.0)	1 (4.0)	-
▪ COPD	**1 (0.8)**	**0 (0)**	**1 (4.0)**	**0.039**
▪ Asthma	4 (3.2)	2 (2.0)	2 (8.0)	0.053
▪ Chronic respiratory disease	1 (0.8)	0 (0)	1 (4.0)	0.361
▪ Tuberculosis	2 (1.6)	1 (1.0)	1 (4.0)	0.180
▪ Cerebrovascular disease	3 (2.4)	1 (1.0)	2 (8.0)	0.056
▪ Chronic kidney disease	**2 (1.6)**	**0 (0)**	**2 (8.0)**	**0.026**
▪ Cancer	1 (0.8)	1 (1.0)	0 (0)	0.361
▪ Other	15 (12.1)	12 (12.1)	3 (12.0)	0.136

The Table 14 reveals significant differences between survivors and deceased patients regarding known comorbidities prior to admission, with a higher proportion of deceased patients having multiple comorbidities ($p = 0.001$). Specifically, chronic kidney disease and COPD were notably more prevalent in deceased patients

Table 15: Comparison of newly discovered comorbidities at admission between survivors and deceased patients

Variable	Total n (%)	Survivors n (%)	Deceased n (%)	p-value
Newly discovered comorbidities at admission	31 (25.0)	25 (25.3)	6 (24.0)	0.628
▪ Hypertension	1 (0.8)	1 (1.0)	0 (0)	-
▪ Diabetes	30 (24.2)	26 (26.3)	4 (16.0)	0.347
▪ Cardiopathy	2 (1.6)	1 (1.0)	1 (4.0)	0.262
▪ COPD	1 (0.8)	1 (1.0)	0 (0)	-
▪ Chronic liver disease	1 (0.8)	0 (0)	1 (4.0)	0.361
▪ Other	1 (0.8)	1 (1.0)	0 (0)	

The Table 15 reveals the analysis of newly discovered comorbidities at admission indicates no significant differences between survivors and deceased patients, with approximately 25% of patients having such comorbidities ($p = 0.628$). Notably, diabetes was the most frequently observed comorbidity.

Table 16: Comparison of the overall comorbidities

Variable	Total n (%)	Survivors n (%)	Deceased n (%)	p-value
Overall comorbidities	104 (83.9)	79 (79.8)	25 (100)	0.055
Overall comorbidities (median, IQR)	2 (1-3)	1 (1-2)	2 (1-3)	0.008
▪ Hypertension	64 (51.6)	50 (50.5)	14 (56.0)	0.495
▪ Diabetes	66 (53.2)	51 (51.5)	15 (60.0)	0.320
▪ Cardiopathy	6 (4.8)	4 (4.0)	2 (8.0)	0.131
▪ COPD	2 (1.6)	1 (1.0)	1 (4.0)	0.180
Overall comorbidities	104 (83.9)	79 (79.8)	25 (100)	0.055

The Table 16 reveals the comparison of overall comorbidities reveals that while a higher percentage of deceased patients (100%) had comorbidities compared to survivors (79.8%), this difference was not statistically significant (p = 0.055). However, the median number of comorbidities was significantly higher in deceased patients (2, IQR: 1-3) compared to survivors (1, IQR: 1-2), suggesting a potential link between the severity of comorbidities and mortality.

Table 17: Comparison of clinical signs at admission between survivors and deceased patients

Variable	Total n (%)	Survivors n (%)	Deceased n (%)	p-value
Systolic Blood Pressure (median, IQR)	125 (110-140)	130 (112-140)	120 (110-140)	0.273
▪ Systolic Blood Pressure < 90 mmHg	1 (0.8)	1 (1.0)	0 (0)	0.104
Diastolic Blood Pressure (median, IQR)	80 (70-90)	80 (70-90)	80 (70-90)	0.926
Temperature (median, IQR) in °C	37.1 (36.6-38.2)	37.1 (36.7-38.2)	37 (36.6-38.1)	0.392
▪ Temperature > 38°C	32 (25.8)	28 (28.3)	4 (16.0)	0.283
Heart Rate (median, IQR) bpm	92 (85-104)	92 (85-102)	92 (84-110)	0.245
▪ Heart Rate > 90 bpm	77 (62.1)	61 (61.6)	16 (64.0)	0.652
Respiratory Rate (median, IQR) cpm	26 (23-30)	25 (22-29)	28 (24-30)	0.072
▪ Respiratory Rate > 20 cpm	118 (95.2)	95 (96.0)	23 (92.0)	0.705
SpO2 % in ambient air (median, IQR)	**88 (82-91)**	**89 (84-91)**	**83 (67-89)**	**0.005**
▪ SpO2 < 90%	**72 (58.1)**	**54 (54.5)**	**18 (72.0)**	**0.004**

The Table 17 reveals the comparison of clinical signs at admission between survivors and deceased patients shows that while values for systolic blood pressure, temperature, heart rate, and respiratory rate did not reveal significant differences, oxygen saturation (SpO2) was significantly lower in deceased patients (83%, IQR: 67-89) compared to survivors (89%, IQR: 84-91) with a p-value of 0.005. Additionally, a higher percentage of deceased patients had SpO2 below 90% (72.0%) compared to survivors (54.5%), highlighting the importance of hypoxemia as a risk factor associated with mortality.

Table 18: Comparison of clinical signs at admission between survivors and deceased patients

Variable	Total n (%)	Survivors n (%)	Deceased n (%)	p-value
Altered consciousness (GCS < 15)	12 (9.7)	6 (6.1)	6 (24.0)	< 0.001
qSofa (n=123)				
▪ qSofa = 0	0 (0.0)	0 (0.0)	0 (0.0)	-
▪ qSofa = 1	20 (16.3)	19 (19.2)	1 (4.0)	0.291
▪ qSofa = 2	83 (67.5)	70 (70.7)	13 (52.0)	0.086
▪ qSofa = 3	20 (16.3)	10 (10.1)	10 (40.0)	0.004
Signs of respiratory distress	22 (17.7)	14 (14.1)	8 (32.0)	0.016
Signs of pneumonia	94 (75.8)	75 (75.8)	19 (76.0)	0.932
Signs of cardiac decompensation	16 (12.9)	8 (8.1)	8 (32.0)	< 0.001
Signs of neurological deficit	3 (2.4)	2 (2.0)	1 (4.0)	0.361

The Table 18 reveals significant differences in altered consciousness and signs of respiratory distress between survivors and deceased patients, with 24% of deceased patients showing altered consciousness (GCS < 15) compared to only 6.1% of survivors, yielding a p-value of less than 0.001. Additionally, signs of respiratory distress were more prevalent among deceased patients (32%) compared to survivors (14.1%), with a p-value of 0.016, indicating a correlation between these clinical features and increased mortality risk.

Table 19: Comparison of laboratory test results at admission between survivors and deceased patients

Variable	Total n (%)	Survivors n (%)	Deceased n (%)	p-value
Hemoglobin (median, IQR) in g/dL (n=116)	14.1 (12.7-15.5)	14.2 (13.0-15.6)	13.7 (12.3-15.0)	0.513
White blood cells (median, IQR) in G/L (n=116)	**9.6 (7.2-14.5)**	**8.0 (5.5-12.0)**	**14.0 (8.5-22.0)**	**0.001**
Neutrophils (median, IQR) in G/L (n=88)	**7.5 (4.7-12.5)**	**7.0 (4.5-10.0)**	**10.5 (6.0-18.0)**	**0.021**
Lymphocytes (median, IQR) in G/L (n=86)	1.3 (0.8-1.9)	1.4 (0.9-2.0)	1.1 (0.7-1.7)	0.287
Platelets (median, IQR) in G/L (n=115)	290 (210-380)	295 (220-400)	270 (200-330)	0.188
CRP (median, IQR) in mg/L (n=111)	50 (12-110)	50 (10-100)	80 (20-140)	0.068
Creatinine (µmol/L) (median, IQR) (n=116)	**95 (78-120)**	**92 (78-115)**	**116 (81-190)**	**0.004**
Urea (mmol/L) (median, IQR) (n=81)	**7.0 (5.0-10.0)**	**6.0 (4.5-8.5)**	**11.0 (7.5-16.0)**	**<0.001**
Glucose (mmol/L) (median, IQR) (n=104)	8.0 (6.0-12.0)	7.8 (5.5-11.0)	9.5 (7.5-17.0)	0.042
D-dimers (median, IQR) (n=75)	800 (400-2000)	700 (400-1800)	950 (500-2500)	0.410

The Table 19 reveals several significant differences between survivors and deceased patients. Notably, deceased patients had higher white blood cell counts and neutrophil levels, indicating a stronger inflammatory response (p = 0.001 and p = 0.021, respectively), while also showing elevated creatinine and urea levels (p = 0.004 and p < 0.001, respectively), suggesting worse renal function; additionally, deceased patients had higher glucose levels (p = 0.042), indicating potential metabolic dysregulation.

Table 20: Comparison of complications during hospitalization between survivors and deceased patients

Variable	Total n (%)	Survivorsn (%)	Deceased n (%)	p-value
All complications	73 (58.9)	56 (56.6)	17 (68.0)	0.174
Number of complications (median, IQR)	1 (0-3)	1 (0-2)	2 (1-4)	0.021
Respiratory deterioration	27 (21.8)	20 (20.2)	7 (28.0)	0.232
Heart failure decompensation	11 (8.9)	6 (6.1)	5 (20.0)	0.061
Acute coronary syndrome	1 (0.8)	1 (1.0)	0 (0.0)	0.316
Cardiac arrhythmia	2 (1.6)	1 (1.0)	1 (4.0)	0.184
Diabetes decompensation	14 (11.3)	9 (9.1)	5 (20.0)	0.091
Diabetic ketoacidosis	**4 (3.2)**	**1 (1.0)**	**3 (12.0)**	**0.033**
Renal failure	**4 (3.2)**	**1 (1.0)**	**3 (12.0)**	**0.033**
Gastrointestinal bleeding	3 (2.4)	2 (2.0)	1 (4.0)	0.589
Shock	9 (7.3)	2 (2.0)	7 (28.0)	<0.001
Infection	6 (4.8)	5 (5.1)	1 (4.0)	0.667
Deterioration of consciousness	9 (7.3)	2 (2.0)	7 (28.0)	<0.001
Seizures	1 (0.8)	0 (0.0)	1 (4.0)	0.316
Agitation	3 (2.4)	1 (1.0)	2 (8.0)	0.123

The Table 20 reveals notable differences between survivors and deceased patients. While the overall number of complications is not significantly different between the groups ($p = 0.174$), deceased patients had a higher median number of complications (2 vs. 1, $p = 0.021$), along with a significantly higher incidence of shock (28.0% vs. 2.0%, $p < 0.001$) and altered consciousness (28.0% vs. 2.0%, $p < 0.001$), suggesting severe complications and a worse prognosis among deceased patients.

3.12 Multivariate Analysis

Table 21: Multivariate analysis using logistic regression of factors identified as significant in univariate analysis

Variables	OR	95% CI	P-value
Arthralgia/Myalgia	**0.2**	**0.0 – 0.8**	**0.022**
Headache	0.6	0.1 – 2.8	0.553
Anosmia	1.2	0.1 – 13.2	0.892
Altered consciousness	1.7	0.3 – 9.6	0.567
Comorbidities known at admission	5.5	0.9 – 32.2	0.057
SpO2 < 90%	4.0	0.9 – 18.4	0.079
Signs of respiratory distress	0.5	0.1 – 2.6	0.449
Signs of heart failure decompensation	**15.2**	**3.2 – 71.4**	**0.001**
Respiratory deterioration	**9.6**	**2.2 – 40.7**	**0.002**
Heart failure decompensation	1.8	0.4 – 9.1	0.457
Renal failure	3.7	0.6 – 22.7	0.157
Shock	35.5	5.3 – 239.0	<0.001
Deterioration of consciousness	**16.1**	**2.9 – 90.6**	**0.002**

The multivariate logistic regression analysis identifies significant factors influencing outcomes, notably that signs of heart failure decompensation (OR 15.2, $p = 0.001$), respiratory deterioration (OR 9.6, $p = 0.002$), and shock (OR 35.5, $p < 0.001$) are strongly associated with increased risk of adverse events, while known comorbidities at admission (OR 5.5, $p = 0.057$) and altered consciousness (OR 16.1, $p = 0.002$) also suggest important prognostic implications, despite some not reaching conventional significance thresholds.

4. Discussion

4.1. Age

The cohort studied had a median age of 58.6 years, indicating that it primarily consisted of adults. Severe cases of COVID-19 predominantly affect adults, particularly older individuals (7). Notably, the median age in our study was lower compared to other research, reflecting the demographic characteristics of the Malagasy population, which is predominantly young. The age distribution in Madagascar reveals a significant proportion of children and young people, with only 4.5% of the population aged 60 and above (8).

Interestingly, our median age aligns closely with findings from a study by Li Q *et al*. conducted in Wuhan, China, which reported a median age of 59 years (IQR: 15-89 years) (9). Comorbidities were identified in 83.4% of our patients, a figure that contrasts with a meta-analysis of 19 studies where only 36.8% of patients had comorbid conditions (10). In contrast, a multicenter prospective study in Argentina, involving 1,909 ventilated patients, reported a comorbidity prevalence of 91.7% (11).

Additionally, our study population was predominantly male, comprising 59.7% of participants. This male predominance may reflect a greater vulnerability to COVID-19, possibly due to a higher prevalence of circulating ACE-2 in men compared to women. This vulnerability is further amplified by the presence of comorbidities among males. Supporting this notion, a meta-analysis of studies in Africa found that 58% of COVID-19 cases were among men (12).

Our results indicate that out of 124 patients, the peak age group was 60-69 years, making up 30.6% of the sample, and 48.4% of the participants were over 60. The gender distribution showed a sex ratio of 1.48, with 59.7% male and 40.3% female participants.

4.2. Clinical signs

The patients in our cohort most frequently reported symptoms such as cough, dyspnea, fever, and arthralgia/myalgia. These signs indicate an infection affecting both the upper and lower respiratory tracts, which can progress to pneumonia and potentially lead to acute respiratory distress syndrome (ARDS). On average, the symptoms lasted about a week before patients were admitted, with dyspnea being the primary reason for hospital visits.

Comparable findings were observed in a study by Huang *et al*. (2019), which analyzed hospitalized patients in China and reported similar common symptoms. In their study, fever was present in 98% of cases, cough in 76%, and myalgia in 44%. They noted that the median time until dyspnea onset was 8 days (IQR: 5-13 days) (13).

4.3. Comorbidities

A notable portion of the patients, specifically 65.32%, presented with one or more comorbidities, with many individuals having two or more health issues. Hypertension and diabetes emerged as the most prevalent conditions in this cohort. Patients with these underlying health issues are considered at greater risk for developing severe COVID-19, likely due to higher circulating levels of ACE-2 in this demographic (14). According to a meta-analysis by Honardoost *et al*. in 2021, hypertension and diabetes are among the most frequently identified comorbidities in those experiencing severe cases of COVID-19 (15). Interestingly, 16.6% of participants in our study had no identifiable comorbidities. In comparison, a retrospective study conducted by Pérez *et al*. involving COVID-19 patients in Malaga, Spain, reported that 38% of their subjects did not have any comorbid conditions (16).

4.4. Additional Examinations

The biological examinations revealed a pronounced inflammatory syndrome in deceased patients, characterized by hyperleukocytosis, predominantly neutrophilic, alongside elevated C-reactive protein (CRP) levels. This heightened inflammatory response may stem from the uncontrollable release of pro-inflammatory cytokines and could suggest the possibility of concurrent bacterial superinfection. In line with findings from Shi *et al*. in 2021, our results indicate that high leukocyte and neutrophil counts are common in severe COVID-19 cases and serve as predictive factors for worse outcomes (17). While we made presumptive diagnoses of bacterial superinfection based on clinical symptoms—such as high fever, purulent sputum, and increased oxygen demands—alongside elevated inflammatory markers, distinguishing true superinfection from disease progression remains challenging.

The practice of administering antibiotics almost universally during COVID-19 has raised concerns about overprescription. A multicenter observational study analyzing data from the SEMICOVID-19 registry found that 87.8% of patients received antibiotics, with higher mortality rates observed among these individuals (18). Additionally, a Cochrane meta-analysis found no significant mortality benefit from azithromycin treatment in hospitalized COVID-19 patients (19).

Moreover, renal function decline was more pronounced in deceased patients, indicated by increased creatinine and plasma urea levels. This deterioration could be attributed to severe hypoxemia, leading to renal cell damage. Previous research suggests that kidney function decline significantly correlates with poor outcomes in COVID-19 (20). In our study, while some patients may have had pre-existing chronic kidney conditions, baseline serum creatinine levels were often unknown.

Interestingly, we did not observe a significant difference in D-dimer levels between survivors and non-survivors, a finding that may be influenced by a lack of measurements in many patients and the limited sample size. A meta-analysis of observational studies showed that elevated D-dimer levels are associated with increased mortality risk in COVID-19 patients (21).

Imaging results revealed that 62.3% of patients underwent chest CT scans, with ground-glass opacities being the predominant finding in 59.7% of cases. Bilateral lung involvement was common, with a significant percentage of patients showing 50-75% pulmonary involvement, indicating potentially severe respiratory conditions. The range of observed lesions further illustrates the respiratory impact of COVID-19.

Our findings underscore the complex interplay between comorbidities, inflammatory responses, and clinical outcomes in COVID-19 patients. The need for cautious interpretation of superinfection diagnoses and the judicious use of antibiotics is paramount, as is recognizing the significant implications of renal function decline in disease severity.

4.5. Mortality

In our study, the hospital mortality rate for patients hospitalized with COVID-19 was 20.17%. This aligns closely with findings from a national retrospective cohort study conducted in Niger, which reported a mortality rate of 15% among 472 patients with severe COVID-19 (22). Similarly, a descriptive cohort study from the Dijon University Hospital in France noted a hospital mortality rate of 16% among 222 patients hospitalized for severe COVID-19 (23). These figures reflect a mortality trend consistent with other studies in both Africa and Europe.

However, it is essential to consider that the actual mortality rate may be underestimated. The ACCOS study, which involved a multicenter, prospective observational cohort of critically ill COVID-19 patients in 64 hospitals across ten African countries, revealed that mortality rates in African countries are higher compared to those reported in studies from Asia, Europe, North America, and South America. This discrepancy is attributed to a lack of adequate intensive care resources and the prevalence of comorbidities such as HIV/AIDS, diabetes, and chronic liver and kidney diseases (5).

Several factors could account for the relatively low mortality rates observed in our study and others from low-income countries. These include underreporting of COVID-19 cases due to limited testing availability and a lack of accurate death reporting, especially for fatalities occurring at home without medical diagnosis. Additionally, the demographic profile of the African population, which is predominantly younger, may influence the incidence and severity of COVID-19 (5).

Among the patients who succumbed in our cohort, the primary cause of death was respiratory distress syndrome resulting from respiratory failure and diffuse alveolar damage. This was exacerbated by insufficient resources for adequate ventilation. Metabolic complications, primarily due to diabetes decompensation, were another significant factor.

Other contributors to mortality included shock, neurological deterioration, and cardiac issues, reflecting the multi-organ failure often observed in severe COVID-19 cases. Elezkurtaj *et al*. (2021) identified respiratory failure due to severe pulmonary infection and alveolar damage as the leading cause of death in autopsied COVID-19 patients, followed by septic shock and multiple organ failure (24). A similar retrospective cohort study at the University Hospital of Michigan found that respiratory distress was the most common cause of death, accounting for 56.1%, while septic shock contributed to 26.8% of fatalities (25).

4.6. Prognostic Factors

This study identified several key prognostic factors associated with hospital mortality in patients with severe and critical COVID-19. Notably, the presence of comorbidities was significantly linked to increased mortality, with the risk escalating when multiple conditions were present. Patients with comorbidities such as hypertension and diabetes were particularly vulnerable due to the associated complications and the dysregulation of the renin-angiotensin-aldosterone system, which raises circulating ACE-2 levels (26).

A retrospective cohort study from New York City involving 3,703 COVID-19 patients found that having more than two comorbidities was associated with a heightened risk of death (OR: 1.90; 95% CI: 1.35-2.68) (30). However, in our study, only chronic obstructive pulmonary disease (COPD) and chronic kidney disease were independently associated with poor outcomes. COPD was notably linked to respiratory failure, which often necessitated intensive care support. A systematic review confirmed that patients with COPD faced a higher risk of severe illness and mortality (RR: 1.88; 95% CI: 1.4-2.4) (27).

Initial respiratory status, indicated by low SpO2 levels and the need for high-concentration oxygen, was also a significant predictor of mortality. Patients with acute respiratory distress syndrome had a markedly increased risk of death (RR: 7.99; CI: 4.9-13) (28). Importantly, while the initial values of oxygen saturation were not predictive of outcomes, the progression of these values over time proved critical. Our findings indicated that a lack of improvement in respiratory status by the seventh day of oxygen therapy significantly correlated with higher mortality rates.

Disorders of consciousness upon admission emerged as another strong predictor of mortality, suggesting severe hypoxic complications such as hypoxic encephalopathy and multi-organ failure. A meta-analysis reinforced this link, indicating that reduced consciousness levels corresponded with increased mortality risk, particularly among patients with Glasgow Coma Scores of 9-14 and below 9 (29).

During hospitalization, numerous complications contributed to mortality, including respiratory decline, cardiac decompensation, and neurological deterioration. These early complications were often associated with the exacerbation of existing chronic conditions. Late complications such as gastrointestinal hemorrhage and cardiocirculatory failure were more prevalent among non-survivors. A meta-analysis identified similar trends, showing that complications like respiratory failure, renal failure, and cardiac issues were common among those who did not survive (30).

Our findings also underscored the significance of recognizing signs of cardiac decompensation, which were strongly linked to increased mortality. The mechanisms underlying this relationship may involve both the exacerbation of pre-existing cardiovascular conditions and direct viral damage to cardiac tissue (31). Interestingly, unlike some other studies, we found no significant impact of male gender on mortality outcomes in our cohort, potentially due to better immune responses observed in women (32).

5. Conclusion

This study highlights the significant mortality associated with severe and critical forms of COVID-19, with a hospital mortality rate of 20.17%. Key prognostic factors identified include the presence of multiple comorbidities, particularly hypertension and diabetes, which increase vulnerability and complicate clinical management. Initial respiratory status, characterized by low oxygen saturation and the need for high-concentration oxygen, proved critical in predicting patient outcomes.

The study also underscores the importance of monitoring for early complications, such as respiratory and cardiac decompensation, which are closely linked to increased mortality. Additionally, disturbances in consciousness upon admission emerged as a strong predictor of poor prognosis, suggesting the need for comprehensive assessments at the time of hospitalization.

These findings emphasize the necessity for targeted interventions and resource allocation in managing patients with severe COVID-19, particularly in low-resource settings. Future research should focus on optimizing treatment protocols and understanding the underlying mechanisms that contribute to mortality in this vulnerable population.

Data availability statement

Data available on the corresponding author upon request

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Funding

No financial support was sought in the production of this article.

References

1. Zhu N, Zhang D, Wang W, *et al*. A novel coronavirus from patients with pneumonia in China, 2019. The New England Journal of Medicine. 2020;382(8):727-733. doi:10.1056/NEJMoa2001017
2. Tessema GA, Kinfu Y, Dachew BA, *et al*. The COVID-19 pandemic and healthcare systems in Africa: A scoping review of preparedness, impact and response. BMJ Global Health; 202:;6(12). doi:10.1136/bmjgh-2021-007179
3. Salyer SJ, Maeda J, Sembuche S, *et al*. The first and second waves of the COVID-19 pandemic in Africa: A cross-sectional study. The Lancet. 2021;397(10281):1265-1275. doi:10.1016/S0140-6736(21)00632-2
4. Okonji EF, Okonji OC, Mukumbang FC, Van Wyk B. Understanding varying COVID-19 mortality rates reported in Africa compared to Europe, Americas, and Asia. Tropical Medicine & International Health. 2021;26(7):716-719. doi:10.1111/tmi.13575
5. Biccard BM, Gopalan PD, Miller M, *et al*. Patient care and clinical outcomes for patients with COVID-19 infection admitted to African high-care or intensive care

units (ACCCOS): A multicentre, prospective, observational cohort study. The Lancet. 2021;397(10288):1885-1894. doi:10.1016/S0140-6736(21)00441-4
6. Randremanana RV, Herindrainy P, Mbotondrasoa F, *et al*. The COVID-19 epidemic in Madagascar: Clinical description and laboratory results of the first wave, March–September 2020. Influenza and Other Respiratory Viruses. 2021;15(4):457-468. doi:10.1111/irv.12845
7. Li J, Huang DQ, Zou B, *et al*. Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. Journal of Medical Virology. 2021;93(3):1449-1458. doi:10.1002/jmv.26424
8. INSTAT Madagascar. Overall results of the general census of population and housing of 2018 of Madagascar (RGPH-3). December 2020;192:33-133.
9. Li Q, Guan X, Wu P, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. The New England Journal of Medicine. 2020;382(13):1199-1207. doi:10.1056/NEJMoa2001316
10. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, *et al*. Clinical, laboratory, and imaging features of COVID-19: A systematic review and meta-analysis. Travel Medicine and Infectious Disease. 2020;34:101623. doi:10.1016/j.tmaid.2020.101623
11. Estenssoro E, Loudet CI, Ríos FG, *et al*. Clinical characteristics and outcomes of invasively ventilated patients with COVID-19 in Argentina (SATICOVID): A prospective, multicentre cohort study. The Lancet Respiratory Medicine. 2021;9(9):989-998. doi:10.1016/S2213-2600(21)00229-0
12. Mohammed M, Sheikh TL, Gidado S, *et al*. Risk factors associated with mortality among patients with novel coronavirus disease (COVID-19) in Africa. Journal of Racial and Ethnic Health Disparities. 2021;8(5):1267-1272. doi:10.1007/s40615-020-00888-3
13. Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
14. Parohan M, Yaghoubi S, Seraji A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality in patients with coronavirus disease 2019 (COVID-19) infection: A systematic review and meta-analysis of observational studies. The Aging Male. 2020;23(5):1416-1424. doi:10.1080/13685538.2020.1774748
15. Honardoost M, Janani L, Aghili R, Emami Z, Khamseh ME. The association between presence of comorbidities and COVID-19 severity: A systematic review and meta-analysis. Cerebrovascular Diseases. 2021;50(2):132-140. doi:10.1159/000513288
16. Martos Pérez F, Sánchez MJ, Sánchez G, *et al*. Comorbidity and prognostic factors on admission in a COVID-19 cohort of a general hospital. Revista Clínica Española (English Edition). 2021;221(9):529-535. doi:10.1016/j.rceng.2020.05.010
17. Shi S, Qin M, Shen B, *et al*. Clinical and laboratory characteristics of severe and non-severe patients with COVID-19: A retrospective cohort study in China. Journal of Clinical Laboratory Analysis. 2021;35(1). doi:10.1002/jcla.23692
18. Bendala Estrada AD, Gil Lamata C, Cueto Pardo C, *et al*. Inadequate use of antibiotics in the COVID-19 era: Effectiveness of antibiotic therapy. BMC Infectious Diseases. 2021;21(1):1144. doi:10.1186/s12879-021-06821-1
19. Popp M, Stegemann M, Riemer M, *et al*. Antibiotics for the treatment of COVID-19. Cochrane Database of Systematic Reviews. 2021;2022(7). doi:10.1002/14651858.CD015025
20. Cheng Y, Luo R, Wang K, *et al*. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney International. 2020;97(5):829-838. doi:10.1016/j.kint.2020.03.005
21. Malik P, Patel U, Mehta D, *et al*. Biomarkers and outcomes of COVID-19 hospitalisations: Systematic review and meta-analysis. BMJ Evidence-Based Medicine. 2021;26(3):107-108. doi:10.1136/bmjebm-2020-111536
22. Katoto PDMC, Brand DA, Kayembe P, *et al*. Clinical features and predictors of mortality among hospitalized patients with COVID-19 in Niger. Conflict and Health. 2021;15(1):89. doi:10.1186/s13031-021-00426-w
23. Sixt T, Thill V, Frotscher F, *et al*. COVID-19: A descriptive cohort of 222 hospitalised patients. Médecine et Maladies Infectieuses. 2020;50(6 Suppl). doi:10.1016/j.medmal.2020.06.120
24. Elezkurtaj S, Greuel S, Ihlow J, *et al*. Causes of death and comorbidities in hospitalized patients with COVID-19. Scientific Reports. 2021;11(1):4263. doi:10.1038/s41598-021-82862-5
25. Ketcham SW, Bolig TC, Molling DJ, Sjoding MW, Flanders SA, Prescott HC. Causes and circumstances of death among patients hospitalized with COVID-19: A retrospective cohort study. Annals of the American Thoracic Society. 2021;18(6):1076-1079. doi:10.1513/AnnalsATS.202011-1381RL
26. Caramelo F, Ferreira N, Oliveiros B. Estimation of risk factors for COVID-19 mortality—Preliminary results. medRxiv. February 25, 2020. doi:10.1101/2020.02.24.20027268
27. Van Gerwen M, Alsen M, Little C, *et al*. Risk factors and outcomes of COVID-19 in New York City; a retrospective cohort study. Journal of Medical Virology. 2021;93(2):907-915. doi:10.1002/jmv.26337
28. Abate SM, Checkol YA, Mantefardo B. Global prevalence and determinants of mortality among patients with COVID-19: A systematic review and meta-analysis. Annals of Medicine and Surgery. 2021;64:102204. doi:10.1016/j.amsu.2021.102204
29. Xiong W, Mu J, Guo J, *et al*. Association of consciousness impairment and mortality in people with COVID-19. Acta Neurologica Scandinavica. 2021;144(3):251-259. doi:10.1111/ane.13471

30. Al-Samkari H, Karp Leaf RS, Dzik WH, *et al*. COVID-19 and coagulation: Bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020;136(4):489-500. doi:10.1182/blood.2020006520
31. Guo T, Fan Y, Chen M, *et al*. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiology. 2020;5(7):811. doi:10.1001/jamacardio.2020.1017
32. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. Clinical Reviews in Allergy & Immunology. 2019;56(3):308-321. doi:10.1007/s12016-017-8648-x