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Risk Factors for Severity and Mortality of Patients Hospitalized for COVID-19 during the 3rd Wave of the Epidemic-Sao Tome and Principe

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Abstract

Rationale: In the literature, some risk factors for severity and mortality from COVID-19 have been indicated. However, these factors can change, depending on the characteristics of the population and health services. In this sense, longitudinal studies can be useful for understanding local realities and subsidizing health actions based on these realities. **Objective:** To analyze the risk factors for severity and death in hospitalized patients with COVID-19. **Methods:** A retrospective cohort of patients with COVID-19 hospitalized from August 1 to October 16, 2021 (3rd wave of the pandemic), notified by the Department of Epidemiological Surveillance of Sao Tome and Principe. We employed measures of strength of associations for the analysis of exposure risk factors. **Results:** We analyzed 110 hospitalized patients (31.8% severe-critical and 68.2% non-severe). The risk factors for severe forms of COVID-19 were: being aged ≥60 years (RR = 3.3), being male (RR = 2), having comorbidities (RR = 2) and the risk increases to 10-fold for multicomorbidities, with emphasis on obesity, neoplasia, skin-muscle-surgical infection, dementia and to some degree CVD. 62.9% of patients with severe forms of the disease were not vaccinated. Risk factors for death among hospitalized and severe/critical cases, respectively, were having comorbidities (RR = 8 and 2.4) multicomorbidities (RR = 10 and 2.8 for those with 2 comorbidities and RR = 33.3 and 4 for those with 3 or 4 comorbidities), especially diabetes, dementia, neoplasia, cutaneous-muscular infection, and obesity. Although CVD was not associated

with risk factors for death, these were the most frequently found among the severely hospitalized and deaths. In addition, important risk factors associated with death were not using corticoids (RR = 3.3, 230-fold risk) and not using anticoagulants-heparin (RR = 1.3, 30% risk) more compared to the severe cases that did use them. Most of the patients who died (63.2%) were not vaccinated. Moreover, having only 1 dose of the vaccine was a risk factor 1.9 times more for death among all hospitalized patients, but in the severe cases, there was no association between the variable vaccination and death. Among those hospitalized with 2 doses, it was a 0.5-fold protective factor among those hospitalized. The *Delta variant* of Sarscov-2 was the one found among severe cases and deaths investigated by genetic sequencing, with more exuberant clinical features compared to the other 2 previous vaccinations. **Conclusion:** Being elderly, male and presenting comorbidities, mainly multicomorbidities were the main characteristics associated with severity of COVID-19. On the other hand, comorbidities, and even worse, multicomorbidities, hospitalization for respiratory failure, lowered level of consciousness, no use of corticoid and no use of anticoagulation in critically ill patients, and not having at least 2 doses of vaccine for covid-19, were characteristics associated with death by COVID-19. These results will help inform healthcare providers so that the best interventions can be implemented to improve outcomes for patients with COVID-19. Public health interventions must be carefully tailored and implemented in these susceptible groups to reduce the risk of mortality in patients with COVID-19 and then the risk of major complications. Intensive and regular follow-up is needed to detect early occurrences of clinical conditions.

Keywords

Covid-19, 3rd Wave of the Epidemic, Risk Factors, Death, Severity, Sao Tomé and Principe

1. Introduction

The new coronavirus broke out in Wuhan, the capital of Hubei province, China, in the month of December 2019, and the virus caused a pandemic since then and has high transmissibility and ability to cause severe cases and deaths [1] [2] [3].

By the end of October 2021, it was responsible for more than 246 million confirmed cases and more than 5 million deaths worldwide. The African continent was the hardest hit, with a number of 8,496,848 cases and 218,004 deaths [4]. Sao Tome and Principe (STP), an island country located in the Gulf of Guinea on the western equatorial coast of Central Africa, has an estimated population of 219,078 people by 2020 [5]. The archipelago has 1 general hospital unit and 7 health centers, distributed among the 7 districts, including a regional one. COVID-19 patients are hospitalized in the Respiratory Symptomatic Service and

in the COVID-19 Campaign Hospital. By the end of October 2021, the country has reported 3714 confirmed cases and 56 deaths [6]. The first notification of COVID-19 in the country is dated April 06, 2020, and the 1st wave of the epidemic in the country happened from April to July/2020 (872 cases/13 deaths), 2nd wave from 30/12/2020 to 31/03/2021 (1202 cases and 18 deaths), and the 3rd wave started in from August to October 19/2021 (1194 cases and 17 deaths). Regarding vaccination against COVID-19, in the country, vaccination will start in March 2021, with campaign activities to cover as much of the population as possible.

The pandemic has drastically affected health services. Worldwide, many kinds of research have been carried out in the search for practices based on scientific evidence, being fundamental to contribute to epidemiological studies aiming at health promotion, disease prevention and hospital care planning, with the identification of individuals subject to risk factors for mortality. In the literature, some risk factors for mortality from COVID-19 have been indicated, such as older age, male gender, lower socioeconomic status, presence of comorbidities (e.g., diabetes mellitus, cardiovascular disease, and cancer, presence of fever, dyspnea, cough, and immunocompromised status), as well as obesity and unhealthy lifestyle, lymphopenia, high levels of C-reactive protein (correlated with the severity of hypoxemia) [7] [8].

However, these factors may change depending on the characteristics of the population and health services, and in this sense, longitudinal follow-up studies can be useful to understand local realities and support health actions based on these realities.

The objective of this research was to analyze the demographic-clinical characteristics and risk factors for severity and death in patients hospitalized with COVID-19 in Sao Tome, São Tome and Principe, in 2021, during the 3rd wave of the epidemic.

2. Materials and Methods

Descriptive cross-sectional retrospective cohort study in STP. The study included all COVID-19 cases hospitalized from August 1, 2021 (start of the 3rd wave) until October 16, 2021.

The diagnosis of the cases of COVID-19 was made by laboratory confirmation. And, Case screening criteria for COVID-19 laboratory testing were done as follows: All patients who sought health care with criteria for hospitalization routinely underwent covid-19 laboratory testing.

For classification of the cases, the following interpretations were used: 1) Not Severe (Asymptomatic: Diagnosis of COVID-19 through positive PCR SARS-Cov-2 test in an individual without symptoms; Mild: Symptoms such as fever, cough, malaise, odynophagia, headache, asthenia/fatigue. No dyspnea and $SatO_2 > 94\%$ and RR < 20/minute; Moderate: $SatO_2 > 94\%$, E: Dyspnea o radiological lesions (< 50% pulmonary infiltrates). Persistent fever is associated with risk factors. RR > 20/minute); 2) Severe (Severe: $SatO_2 < 94\%$ or RR > 30/min. Has

pulmonary compromise > 50%; Critical: Neurological alteration ✓ dyspnea ✓ MAP < 65, ✓ lactate > 2 ✓ Patient in respiratory failure requiring mechanical ventilation ✓ Patient in shock or vascular collapse).

Continuous variables were analyzed by measures of central tendency (minimum, mean, median, maximum, and standard deviation); categorical variables were described by absolute (n) and relative (%) frequency.

Risk factors for severity and death were analyzed using association measures (Relative Risk). To estimate the incidence of severity we used the following variables: sex, age group, district of residence and comorbidities (presence of comorbidities, number of comorbidities and type of comorbidities). To estimate the incidence of death among all cases and among severe cases, the following variables were used: sex, age group, district of residence and comorbidities (presence of comorbidities, number of comorbidities and type of comorbidities), vaccination status and use of antibiotics. In addition, among the severe cases, we used the variables: use of corticoids and use of anticoagulants. Results with relative risk values equal to 1 were interpreted as no association; for results with a relative risk value greater than 1, it was interpreted that the variable studied was associated with the risk factor for severity and/or death; and for results with relative risk values less than 1, it was interpreted that the variable studied was not associated with the risk factor for severity and/or death.

This scientific study was approved by the Research Ethics Committee of the Sao Tome and Principe Ministry of Health, and the study was previously authorized by those responsible at Dr. Ayres de Menezes Central Hospital and COVID-19 Campaign Hospital in October 2021. Due to the use of secondary data, patients/relatives did not need to sign the Informed Consent Form.

3. Results

3.1. General Demographic Characteristics

A total of 110 patients were analyzed, 52.7% (n = 58) of whom were women, with a median age of 69 years with a range from 21 days old to 93 years old. 31.8% (n = 35) were identified as severe cases and 68.2% (n = 75) were non-severe cases at admission or evolution (Table 1).

The severe cases were more prevalent in male patients (65.7%-n = 23) while the non-severe cases were more prevalent in female patients (61.3%-n = 46). The median age for severe cases was 69 years PD (19.8 years), while for non-severe cases it was 51 years PD (19.1 years). 71.4% (n = 25) of the patients who presented severe form, was 60 years of age, while 48% (n = 36) who presented non-severe forms were less than 50 years of age (Table 1).

60% (n = 66) of patients resided in the Água Grande district and 21.8% (n = 24) in Mezóchi district. The Autonomous Region of Príncipe with 0.9% (n = 1) was the district with the lowest number of hospitalized cases (Table 1).

By the target group, 62.9% (n = 22) and 72% (n = 54) of severe and non-severe patients respectively were not vaccinated for COVID-19. 31.4% (n = 11) and 10.7%

Table 1. General demographic characteristics of hospitalized patients.

Characteristics of patients	General hospitalized (n = 110)	Not serious (n = 75)	Severe/critical (n = 35)	Severe/critical who died (n = 19)
Sex (n and %)				
-Male	52 (47.3%)	29 (38.7%)	23 (65.7%)	13 (68.4%)
-Female	58 (52.7%)	46 (61.3%)	12 (34.3%)	6 (31.6%)
Median age (years)	69 (21 d - 93)	51 (17m - 89) DP (19.1)	69 (21d - 93) DP (19.8)	70 (18 - 91) DP (17.3)
Age range (years):				
-Under 50years	42 (38.2%)	36 (48%)	6 (17.1%)	3 (15.8%)
-50 to 59 years old	20 (18.2%)	16 (21.3%)	4 (11.4%)	2 (10.5%)
-60 years or older	48 (43.6%)	23 (30.7%)	25 (71.4%)	14 (73.7%)
Districts (n and %)				
-Água Grande	66 (60%)	46 (61.3%)	20 (37.1%)	11 (57.9%)
-Mezóchi	24 (21.8%)	15 (20%)	9 (25.7%)	6 (31.6%)
-Cantagalo	8 (7.2%)	5 (6.7%)	3 (8.6%)	2 (10.5%)
-Lobata	11 (10%)	8 (10.7%)	3 (8.6%)	0
-RAP	1 (0.9%)	1 (1.3%)	0	0
Vaccination status:				
-Vaccinated	19 (17.2%)	8 (10.7%)	11 (31.4%)	7 (36.8%)
-Not vaccinated	76 (69.1%)	54 (72%)	22 (62.9%)	12 (63.2%)
-Unknown	13 (11.8%)	12 (16%)	1 (2.9%)	0
-Non-target group	2 (1.8%)	1 (1.3%)	1 (2.9%)	0
Vaccine doses:				
-Complete + 14 days	11 (10%)	4 (5.3%)	7 (20%)	3 (15.7%)
-Complete - 14 days	0	0	0	0
-Complete + 14 days	4 (3.6%)	2 (2.7%)	2 (5.7%)	1 (5.3%)
-Incomplete - 14 days	4 (3.6%)	2 (2.7%)	2 (5.7%)	3 (15.7%)
-Not vaccinated	76 (69.1%)	54 (72%)	22 (62.9%)	12 (63.25)
-Unknown	13 (11.8%)	12 (16%)	1 (2.9%)	0
-Non-target group	2 (1.8%)	1 (1.3%)	1 (2.9%)	0
No. Comorbidities:				
-None	33 (30%)	29 (38.7%)	4 (11.4%)	1 (5.3%)
-1 co-morbidity	56 (50.9%)	37 (49.3%)	19 (54.3%)	9 (47.4%)
-2 co-morbidity	15 (13.6%)	8 (10.7%)	7 (20%)	5 (26.3%)
-3 co-morbidity	2 (1.8%)	0	2 (5.7%)	2 (10.5%)
-4 co-morbidity	2 (1.8%)	0	2 (5.7%)	2 (10.5%)
-Unknown	1 (0.9%)	1 (1.3%)	0	0

Continued

Comorbidities:				
-Hypertension	37 (33.6%)	18 (24%)	19 (54.3%)	12 (63.2%)
-Diabetes	15 (13.6%)	7 (9.3%)	8 (22.9%)	8 (42.1%)
-STROKE	3 (2.7%)	0	3 (8.6%)	3 (15.8%)
-Asthma/COPD	4 (3.6%)	3 (4%)	1 (2.9%)	0
-Dementia	1 (0.9%)	0	1 (2.9%)	1 (5.3%)
-HIV	2 (1.8%)	1 (1.3%)	1 (2.9%)	0
-Testicular infection-trauma	1 (0.9%)	0	1 (2.9%)	1 (5.3%)
-Cardiopathy	3 (2.7%)	1 (1.3%)	2 (5.7%)	1 (5.3%)
-Psychiatric	6 (5.5%)	5 (6.7%)	1 (2.9%)	1 (5.3%)
-Neoplasia	1 (0.9%)	0	1 (2.9%)	1 (5.3%)
-Obesity	7 (6.4%)	1 (1.3%)	6 (11.1%)	5 (26.3%)
-Venous insufflation/ulcer	2 (1.8%)	1 (1.3%)	1 (2.9%)	1 (5.3%)
-Alcoholism	4 (3.6%)	3 (4%)	1 (2.9%)	0
-None	33 (30%)	29 (28%)	4 (11.4%)	1 (5.3%)
-Drepanocytosis	1 (0.9%)	1 (1.3%	0	0
More risk factors:				
-Surgeries	1 (0.9%)	0	1 (2.9%)	1 (5.3%)
-SPSPT	1 0.9%)	0	1 (2.9%)	1 (5.3%)
-Newborn	1 0.9%)	0	1 (2.9%)	0
-pregnant	2 (1.8%)	2 (2.7%)	0	0
-Hospitalization	1 0.9%)	0	1 (2.9%)	1 (5.3%)

(n = 8) of the severe and non-severe cases respectively were vaccinated for covid-19, and of these, 20% (n = 7) of the severe patients had the full dose of vaccine, while only 2.7% (n = 2) of the non-severe cases had full vaccination. 20% of the severe had completed vaccination of more than 14 days while 11.4% of this group had incomplete/less than 14 days of vaccination (Table 1).

70% (n = 77) of patients had at least 1 comorbidity, 88.6% (n = 31) severe and 61.3% (n = 46) non-severe. Compared to the non-severe cases, 88.6% (n = 31) of the severe patients had more comorbidities, including hypertension (54.3% vs 24%), diabetes (22.9% vs 9.3%), overweight/obesity (11.1% vs 1.3%), stroke (8.6% vs 0), respectively. On the other hand, non-severe patients had more psychiatric comorbidities compared to severe cases (6.7% vs 2.9%). Overall, the least frequent comorbidities were cardiopathy, dementia, neoplasia and drepanocytosis with 0.9% (n = 1) each. Other associated factors were pregnancy with 1.8% (n = 2), newborn, and cutaneous-muscular infection with the need for surgical intervention associated with prolonged post-surgery statism accumulating at 1.8% (n = 2). While the non-severe cases had 1 to 2 comorbidities, the severe cases had 3 to 4 associated comorbidities (Table 1).

The main cause of admission for the severe/critical cases was respiratory failure with 71.4% (n = 25), followed by lowered level of consciousness with 20% (n

= 7). Less frequent were cutaneous-muscular infections, asthenia and groaning/refusal to eat with 8.7% (n = 3). Acute influenza with 36% (n = 27) was the most frequent cause of hospitalization among the non-severe cases, followed by dyspnea with 25.3% (n = 19), asthenia with 16% (n = 12) and decompensation of liver disease in 8% (n = 6) patients (Table 2).

Table 2. Clinical characteristics.

Characteristics of patients	General hospitalized (n = 110)	Not serious (n = 75)	Severe/critical (n = 35)	Severe/critical who died (n = 19)
Cause of hospitalization				
-Respiratory failure	25 (22.7%)	0	25 (71.4%)	13 (68.4%)
-Lowered consciousness	8 (7.3%)	1 (1.3%)	7 (20%)	5 (26.3%)
-Forner gangrene	1 (0.9%)	0	1 (2.9%)	1 (5.3%)
-Asthenia	13 (11.8%)	12 (16%)	1 (2.9%)	0
-Gemitus/refusal of food-dyspnea	1 (0.9%)	0	1 (2.9%)	0
-dyspnea	19 (17.3%)	19 (25.3%)	0	0
-acute influenza	27 (24.5%)	27 (36%)	0	0
-Hepatopathy	6 (5.5%)	6 (8%)	0	0
-abdominal pain	3 (2.7%)	3 (4%)	0	0
-Cellulitis	1 (0.9%)	1 (1.3%)	0	0
-Anemia	1 (0.9%)	1 (1.3%)	0	0
-chest pain	1 (0.9%)	1 (1.3%)	0	0
-DM/HTA decompensation	1 (0.9%)	1 (1.3%)	0	0
-Dehydration	1 (0.9%)	1 (1.3%)	0	0
-Paludism	1 (0.9%)	1 (1.3%)	0	0
-Asymptomatic	1 (0.9%)	1 (1.3%)	0	0
Average time between clinic onset and hospitalization (days)	4.8 (0 - 14)	5.3 (1 - 14)	4.5 (0 - 10)	4.5 (0 - 10)
T. of symptom onset-hospitalization:				
<24 h	5 (4.5%)	3 (4%)		
48 - 72 h	35 (31.8%)	21 (28%)	2 (5.7%)	1 (5.3%)
4 - 7 days	55 (50%)	39 (52%)	14 (40%)	10 (52.6%)
8 - 14 days	13 (11.8%)	10 (13.3%)	16 (45.7%)	5 (26.3%)
Unknown	2 (1.8%)	2 (2.7%)	3 (8.6%)	3 (15.8%)
Radiological description:				
-Bilateral infiltrate	39 (35.5%)	22 (29.3%)	17 (48.6%)	10 (52.6%)
-Unknown	10 (9.1%)	0	10 (28.6/)	4 (21.1%)
-Not done	57 (51.8%)	50 (66.7%)	7 (20%)	5 (26.3%)
-Normal	2 (1.8%)	1 (1.3%)	1 (2.9%)	0
-Unilateral infiltrate	2 (1.8%)	2 (2.7%)	0	0

Continued

Laboratory tests:				
-Leukocytosis and lymphopenia	9 (8.1%)	4 (5.3%)	5 (14.3%)	5 (26.3%)
-Normal	2 (1.8%)	2 (2.7%)	0	0
-Not done	99 (90%)	69 (92%)	30 (85.7%)	14 (73.6%)
Antibiotic therapy:				
-Ceftriaxone	54 (49.1%)	20 (26.7%)	34 (97.1%)	19 (100%)
-Cefotaxime	5 (4.5%)	2 (2.7%)	3 (8.6%)	1 (5.3%)
-Azitromicina	50 (45.5%)	29 +1 (40%)	20 (57.1%)	11 (57.9%)
-Clavamox	33 (30%)	24 +3 (36%)	6 (17.1%)	2 (10.5%)
-Amicacina	2 (1.8%)	0	2 (5.7%)	2 (10.5%)
-Metronidazol	6 (5.5%)	4 (5.3%)	2 (5.7%)	1 (5.3%)

The mean time between clinic onset and hospitalization was 4.8 days ranging from zero to 14 days. And 50% (n = 55) of patients were hospitalized between 4 and 7 days after disease onset (Table 2).

48.6% (n = 17) of the severe/critical cases showed bilateral lung changes on chest radiography. Although most of the non-severe cases did not have radiography, 29.3% (n = 22) also showed bilateral radiological lesions (Table 2). 90% (n = 99) of patients did not have monitoring laboratory tests. 8.1% (n = 9) had lymphopenia (Table 2). Of the cases analyzed by genetic sequencing, the Delta variant of Sarscov-2 was found exclusively.

Laboratorially, the Delta variant of Sarscov-2 was the one found among severe cases and deaths investigated.

All patients received at least one dose of antibiotic therapy empirically, with ceftriaxone, azithromycin and amoxicillin/clavulanate being the most commonly used (49.1%; 45.5% and 33%, respectively (Table 3).

71.4% (n = 25) of the critically ill patients received corticosteroids (mostly dexamethasone) and 48.6% received anticoagulants (enoxaparin). The mean time between hospitalization and initiation of corticoid was 1.2 days and for thrombolytic was 1.6 days. The medical time between onset and severity was 4, 2 days, and hospitalization was 1 (0-6) days, with the majority 26 (74.3%) hospitalized within 24 hours of the onset of severity (Table 3).

Of the 110 hospitalized patients, there were 17.3% (n = 19) hospital deaths, that is, 54.3% of the severe/critical cases. The mean time between hospitalization and death was 5.3 days, with the majority, *i.e.*, 36.8% of deaths occurring within the first 24 hrs and 1 (5.3%) occurring after 14 days. The most common cause of death was respiratory failure 17.3% (n = 19), followed by associations: neurological injury/encephalopathy with 3.6% (n = 4), (shock 1.8% (n = 2), acute renal failure 0.9% (n = 1) and embolism 0.9% (n = 1) (Table 4).

3.2. Factors Associated with Disease Severity

Of the 110 patients hospitalized with COVID-19, 35 (31.8%) had severe disease.

The factors associated with severity were: being male (RR = 2), age ≥ 60 years (RR = 3.3), having comorbidities (RR = 2), and increases to 10-fold for 3 or 4 comorbidities. Cardiovascular diseases and diabetes were the most frequent comorbidities in hospitalized patients; however, there was no association

Table 3. Clinical characteristics/management of severe cases.

Characteristics	Severe/critical patients (n = 35)	Severe patients who died (n = 19)
Antibiotic therapy:		
-Ceftriaxone	34 (97.1%)	19 (100%)
-Cefotaxime	3 (8.6%)	1 (5.3%)
-Azitromicin	20 (57.1%)	11 (57.9%)
-Clavamox	6 (17.1%)	2 (10.5%)
-Amikacin	2 (5.7%)	2 (10.5%)
-Metronidazol	2 (5.7%)	1 (5.3%)
Dexametasone	25 (71.4%)	9 (47.4%)
Sem dexametasona	10 (28.6%)	10 (52.6%)
Mean time between hospitalization and start of dexamethasone (days)	1.2 (0 - 8)	1.1 (0 - 3)
Enoxaparin	17 (48.6%)	7 (36.8%)
No enoxaparin	18 (51.4%	12 (63.2%)
Mean time between hospitalization and initiation of enoxaparin (days)	1.6 (0 - 8)	2.4 (0 - 8)
Mean time between disease onset and severity	4. 2 (1 - 9) dias	4 (1 - 9) dias
Onset of disease and severity		
<24 h	3 (8.6%)	2 (10.5%)
48 - 72 h	11 (31.4%)	8 (42.1%)
4 - 7 days	19 (54.3%)	7 (36.8%)
8 - 14 days	2 (5.7%)	2 (10.5%)
Over 14 days	0	0
Mean time between hospitalization and severity (days)	1 (0 - 6)	1.4 (0 - 6)
Hospitalization and severity (n)		
<24 h	26 (74.3%)	12 (63.2%)
48 - 72 h	7 (20%)	5 (26.3%)
4 - 7days	2 (5.7%)	2 (10.5%)
8 - 14 days	0	0
Over 14 days	0	0
Complications:		
Respiratory failure	21 (60%)	19 (100%)
Shock	3 (8.6%)	2 (10.5%)
Neurological picture/convulsion	5 (14.3%)	4 (21.1%)
Embolism	1 (2.9%)	1 (5.3%)

Table 4. Deaths and their relations.

Deaths and their relations	
Mean time between hospitalization and death	5.3 (0 - 16) days
Time between hospitalization and death (days):	
-Up to 24 h	7 (36.8%)
-48 to 72h	1 (5.3%)
-4 to 7 days	5 (26.3%)
-8 to 14 days	5 (26.3%)
-Over 14 days	1 (5.3%)
Causes of death:	
-Acute respiratory insufficiency (SARS)	19 (100%)
Associations with insufficiency:	
-Neurological Picture of Stroke	4 (21.1%)
-Septic shock	2 (10.5%)
-Pulmonary Thromboembolism	1 (5.3%)
-Acute renal insufficiency	1 (5.3%)

between these in relation to the classification regarding the severity of the cases. Patients living in the district of Cantagalo were those with the highest risk of severity, on the order of 20% more in relation to residents in other districts (Table 5).

Dyspnea without desaturation, acute influenza, hepatopathy, abdominal pain, cellulitis, anemia, chest pain, decompensation of diabetes/hypertension, malaria and asymptomatic cases: it was not associated with severe forms.

62.9% of patients presenting severe forms of the disease were not vaccinated, but there was no association between hospitalized patients as the incidence between severe and non-severe cases.

3.3. Factors Associated with Mortality

Of 110 patients in the cohort, 17.3% (n = 19) died, *i.e.*, 54.3% of critically ill patients, of whom 73.7% (n = 14) were ≥ 60 years old, 15.8% (n = 3) people younger than 50 years old, and 10.5% (n = 2) people between 50 and 59 years old.

Among all hospitalized patients, had higher risk of occurrence of death from COVID-19 male patients (RR = 2.5), but, the adjusted relative risk for death among severe cases, there was almost no risk-risk association between genders (RR = 1.1 and 0.9 for both genders). In addition, being ≥ 60 years old (RR of 3.6) compared to those younger than 60 years. On the other hand, among severe cases, the following were associated: being residents of the districts of Mé-zochi and Cantagalo (RR = 1.3 and 1.2), comorbidities (RR = 8), with more than 1 comorbidity, the risk was 2 to 33.3 times more. Among severe cases, the risk is 2.4 times more, increasing to 4 times in 3 or 4 comorbidities. The comorbidities that

Table 5. Risk factors associated with severity of COVID-19.

Characteristics	Relative Risk for Severity
Sex	
-Male	2
-Female	0.5
Age Group	
-Under 60 years old	0.3
-60 years or older	3.3
-50 to 59 years old	0.4
-60 years or more	2.5
Under 50 years old	0.2
-60 years or older	5
Under 50 years old	0.5
-50 to 59 years old	2
District of residence	
Água grande	1
Mezóchi	1.1
Cantagalo	1.2
Lobata	0.9
RAP	0
No. of Comorbidities	
No comorbidity	0.2
With comorbidities	2
No. of Comorbidities	
1 co-morbidity	0.5
More than 1 comorbidity	2
No. of Comorbidities	
No comorbidity	0.2
With 2 comorbidities	2.5
No. of Comorbidities	
No comorbidity	0.1
With 3 or 4 comorbidities	10
Comorbidities	
-Cardiovascular disease (CVD).	1.1
-Diabetes Melittus	1
-Asthma/COPD	0.5
-Dementia	2
-HIV	1
-Psychiatric disorder	0.02
-Obesity	1.7
-Neoplasia	2
-Alcohol	0.5
-Testicular-surgical infection	2

CVD: hypertension, stroke, heart disease and vascular insufficiency; COPD: Chronic Obstructive Pulmonary Disease.

were associated with the risk of death were diabetes, dementia, cancer, testicular infection, and obesity, but obesity was not associated with the severe cases of death.

There was no association for death in relation to the use or non-use of antibiotic type (Table 6).

Of the 71.4% (n = 25) who took corticoids, 64% (n = 16) survived and 36% (n = 9) died. All other (10 patients) severely ill who did not take corticoids progressed to death. Corticoid use was associated with lower mortality and for those who did not take corticoids the risk of dying was 3.3 more compared to those who took corticoids (Figure 1 and Table 6).

Table 6. Risk factors associated with death in patients with COVID-19.

Characteristics	Relative Risk for Deaths Among General	Relative risk of death among the severely ill
Sex		
Male	2.5	1.1
Female	0.4	0.9
Age Group		
Under 50 years old	0.3	0.9
50 - 59 years old	0.5	0.9
60 years or older	3.6	1.1
<60 years old	0.2	0.9
≥60 years old	3.6	1.1
50 - 59 years old	0.3	0.9
>60 years old	2.9	1.1
Under 50 years old	0.2	0.9
≥60 years old	4.1	1.1
Under 50 years old	0.2	1
50 - 59 years old	4.1	1
District of Residence		
Água Grande	0.8	1
Mezochi	1.6	1.3
Cantagalo	1.6	1.2
Lobata	0	0
Vaccination status		
Vaccinated 1 dose		
Not vaccinated		
Vaccinated 2 doses		
Not vaccinated		
2 vaccine doses or single dose	0.5	0.4
1 vaccine dose	1.9	0.2

Continued

N° of Comorbidities		
N° of Comorbidities:		
No comorbidity	0.1	0.4
With comorbidities	8	2.4
1 comorbidity	0.3	0.5
More than 1 comorbidity	2.9	1.7
No comorbidities	0.09	0.3
2 comorbidities	10	2.8
No comorbidities	0.03	0.25
3 or 4 comorbidities	33.3	4
Comorbities	**RR for death among hospitalists**	**RR for death among the severely ill**
Cardiovascular Diseases (CVD)	0.8	0.9
Diabetes mellitus	1.4	1.5
Asthma/COPD	0	0
HIV	0	0
Dementia	2.6	1.4
Neoplasia	2.6	1.4
Testicular infection-surgery	2.6	1.4
Psychiatric disorder	0.4	1.4
Obesity	1.9	1.1
Alcoholism	0	0
Antibiotics		
Ceftriaxone	1.9	1
Cefotaxime	0.2	1
Azithromycin/erythromycin	0.9	1
Amoxicillin/clavulonate	0.2	1
Thrombolytic/anticoagulant		
Enoxaparin	-	0.6
Without enoxaparin	-	1.3
Corticoids		
Dexamethasone	-	0.3
Without Dexamethasone	-	3.3

CVD: Hypertension sisteêmcia, Stroke, heart disease, venous insufficiency; COPD: Chronic Obstructive Pulmonary Disease.

On the other hand of the 48.6% (n = 17) who received enoxaparin, 58.8% (n = 10) survived, 36.8% (n = 7) died. All other 12 critically ill patients who did not

receive enoxaparin, died (Figure 1). The use of enoxaparin was associated with lower mortality and for those who did not take enoxaparin, the risk was 1.3 (Figure 2) (Table 6).

4. Discussion

The results of the present study demonstrated which are the main risk factors associated with a higher risk of severe forms and death from COVID-19 in STP, among the factors evaluated, bringing important subsidies for clinical decision making, since they allow the recognition of factors associated with the prognosis of the disease at the time of identification of the case by the health system.

Risk of severity:

In the present study, the following were identified as risk factors associated with severe forms of the disease: male gender, ≥60 years and comorbidities.

Regarding gender and age group, old age and males sex had 3.3 and 2.5 times higher risks, respectively, in developing severe forms of the disease compared to people ≥60 years old and female sex. This association between old age and

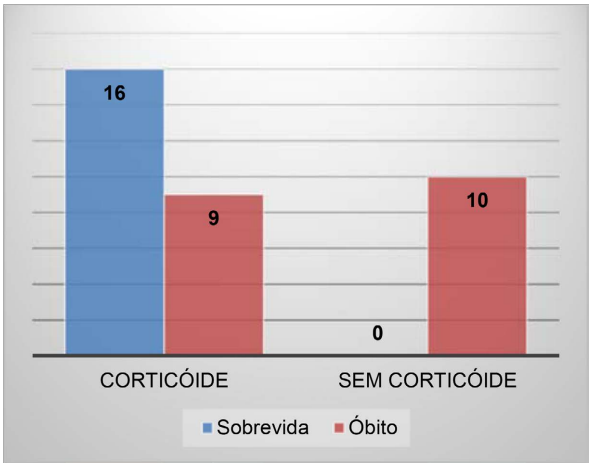

Figure 1. Use of corticoids in severe cases of COVID-19 in Sao Tome and Príncipe.

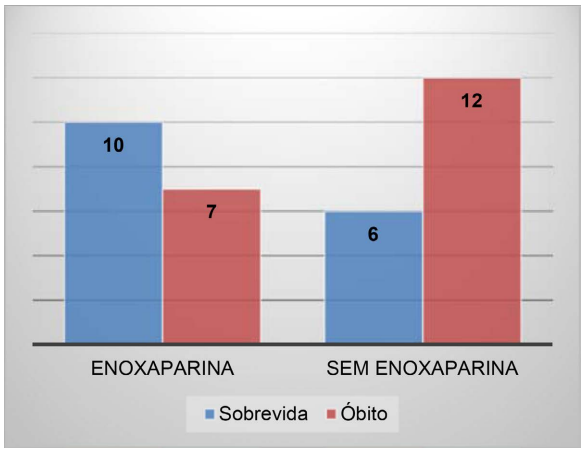

Figure 2. Enoxaparin use X death and survival—Severe cases of COVID-19 in Sao Tome and Príncipe.

severe symptoms of COVID-19 have been observed in several clinical studies [7] [9] and [10]. One justification for this may be some age-related chronic medical conditions and/or lower levels of immunity [7] [11] [12]. In addition, aging affects T cell, and B cell functions [8]. This reduction is associated with impaired responses to viral infections such as influenza [13] and excess cytokine production can lead to prolonged pro-inflammatory immune responses and therefore perhaps contribute to unsatisfactory outcomes.

One reason for the advantages in women can be justified as follows: within the adaptive immune system, men have lower T-cell numbers and decreased B-cell production compared to women [11] [12] [13] [14].

In clinical observation, the existence of comorbidities contributed to a 2-fold increase in severe cases, and the risk of severity was 10 times higher for people with multicomorbidities, with emphasis on surgical infection, dementia, neoplasia, and obesity, at up to 2 times higher, and at lower risk, CVD. The presence of comorbidity in patients with COVID-19 already represents a risk factor, and correlates with worse prognosis as stated in the study by Souza *et al.* in 2021 [15] [16].

This study showed a frequency of 6.4% cases of obesity among hospitalized patients, of which 11.1% had severe forms, raising a risk of 70% more in association with the severe form of covid-19. Developed countries have identified a prevalence of obesity close to 40% and 6.2%. In another, a significant association was demonstrated between obesity prevalence and severe SARS by COVID-19, suggesting that obesity may be a risk factor for severe disease progression and, consequently, a greater risk of admission to the Intensive Care Unit. It was seen that high body mass index among individuals of young-adult age puts the younger population at risk, since adipose tissue serves as a reservoir for the virus. Studies have reported that diabetes is a determinant of severity and mortality in COVID-19 patients [17] [18] [19] [20] [21].

It was observed that women, people below 60 years of age, people without any comorbidities had a lower risk of developing severe form of COVID-19.

Risk of death:

Referring to death, the following were identified as risk factors for death among all those hospitalized for COVID-19: male gender, ≥60 years, presence of comorbidities, worsening to multimorbidity, with emphasis on diabetes mellitus, dementia, neoplasia, testicular infection, and obesity. When adjusted, the following were identified as risk factors for death among severe cases by COVID-19: presence of comorbidities, worsening to multimorbidity, especially diabetes mellitus, dementia, neoplasia, and cutaneous-muscle-surgical infection; non-use of corticoid (dexamethasone) and anticoagulant (heparin).

Regarding gender, men had a lower cumulative survival probability than women, as well as a higher risk of death than hospitalized women. As already noted, a systematic review with meta-analysis showed that men represent 60% of patients with COVID-19, suggesting greater susceptibility to virus infection in

this population. As already justified, and further reported in the study by Takahashi *et al.* (2020), analyzing the immune response in different sexes, it was found that male patients have an increase in inflammatory cytokines (IL-8, IL-18, CCL5); moreover, it was also found that during the course of the disease, men have a lower activation of the number of T cells. Males also show a more prolonged viral RNA clearance compared to females [22] [23]. Porto (2021) reported that the lower incidence of death in females may be related to estrogen, which can better stimulate immunity and respond better to vaccines [24].

This finding, besides having clinical relevance in relation to the prognosis of the disease, also has relevance for health policy, considering that men historically have less access to health services. Moreover, the higher probability of death in men can be explained by the fact that they seek health services in more severe cases [25]. But among severe cases, there was practically no difference in relation to gender.

Regarding age group, of all those hospitalized, it was observed that the elderly >60 years old had a 3.6 times higher risk of dying from COVID-19 than patients younger than 60 years old. IN STP, since the beginning of the pandemic, elderly individuals have been observed to represent the highest percentage of COVID-19 deaths (Sitrep). But among severe cases, there was no association regarding age > 60 years or >60 years for death. Similarly, age "60 years presented a 3.6-fold risk for death in multivariate analysis, but in terms of severity, there is no difference regarding age group for death. Although, the highest number of hospitalized cases, as well as severe cases and death were people" 60 years old, and the highest number of severe cases.

Comorbidity was the main factor in the association with mortality. Individuals aged over 60 years had at least one comorbidity, which justifies this population composing the risk group for COVID-19, placing this population more prone to the damages of pandemic situations. This information is feasible for adjustment of public policies for integrating the elderly into society, and analysis of the difficulty of access and health care, making it necessary to strengthen the program to improve the quality of life for the elderly.

Moreover, the presence of comorbidity increases the chance of death by about 9 times, compared to patients without comorbidities [26]. In a systematic review of 11 studies, it was observed that the prevalence of chronic diseases (cardiovascular diseases, pulmonary diseases, hypertension, diabetes, and kidney disease) are associated with the worst prognosis in COVID-19 patients, as well as being associated with a high risk of death [27].

Our study showed no association between antibiotic type and mortality, and all critically ill patients underwent antibiotic use. The WHO recommends empiric use of antibiotics in patients diagnosed with COVID-19 should be initiated if bacterial coinfection or sepsis is suspected (WHO, 2021).

Regarding thromboembolic prophylaxis, of all severe cases, it was observed that those who did not receive enoxaparin had a 1.3 times higher risk of dying from covid-19 than patients who received enoxaparin, including the develop-

ment of thromboembolism. The literature strongly recommends this for patients hospitalized with COVID-19.

Of all the severe cases, it was seen that those who did not use corticosteroids had a 3.3 times greater risk of dying compared to those who did. Corticosteroids exert their anti-inflammatory and immunosuppressive activity by interfering in different steps of immune system regulation [28]. Several studies have shown that hospitalized patients treated with dexamethasone showed a benefit in relation to mortality, when compared to patients under conventional treatment. One study, 63 (36.8%) of hospitalized patients required respiratory support, while, 1129 (9.4%) of patients who did not receive dexamethasone required respiratory support. Among patients who required respiratory support for the mortality outcome, the authors found a significant association between dexamethasone use and reduced mortality in two analyses performed - both unadjusted (HR 0.40 to 0.87) and primary multivariable Cox regression analysis (HR 0.46 to 0.96). Patients with severe forms of COVID-19 may exhibit a systemic inflammatory response capable of damaging the lung and other organs. For this reason, it has been proposed that the use of corticosteroids could prevent or mitigate this deleterious effect. The RECOVERY multicenter randomized trial conducted in England showed a reduction in mortality in the group of hospitalized patients who received dexamethasone. However, this difference was only significant in those who were requiring mechanical ventilation in RECOVERY, 2021 [29].

Our study demonstrated that 62.9% (n = 22) and 72% (n = 54) of critically ill and non-severe patients, respectively, were not vaccinated for covid-19. This study showed that there was no association of evolution to death among the cases once they were hospitalized.

Vaccination is known to prevent hospitalization for COVID-19 cases. Several studies have shown that most deaths, *i.e.*, about 75% of COVID-19 deaths recorded in the first 10 months of 2021 occurred in individuals who were not immunized against the disease [30] [31] [32] [33] [34].

Although this study covers the totality of hospitalized cases identified throughout the island (size in the country), giving to understand the reality of the country, our study has some limitations:

First, the sampling diversity was very small that may not recognize the possible factors affecting severity and mortality from COVID-19;

Second, the literature on coronaviruses continues to accumulate, new information and new articles published frequently;

Third, the unavailability of laboratory tests, it has not been possible to characterize all the factors involved in the inflammation cascade for COVID-19.

Absence of studies from countries similar to Sao Tome e Principe for comparison purposes.

5. Conclusion

It was concluded that being elderly, male and presenting comorbidities were the

main risk factors associated with severity of COVID-19. On the other hand, comorbidities, especially, multicomorbidities, non-use of corticoids in critically ill patients, non-use of anticoagulation in critically ill patients, were characteristics associated with death by COVID-19. These results will help inform healthcare providers so that the best interventions can be implemented to improve the outcomes of Covid-19 patients. Of emphasis, public health interventions must be carefully tailored and implemented in these susceptible groups to reduce the risk of mortality in patients with COVID-19 and then the risk of major complications. Intensive and regular follow-up is needed to detect early occurrences of clinical conditions.

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Conflicts of Interest

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

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