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Factors predicting in-hospital all-cause mortality in COVID 19 patients at the Laquintinie Hospital Douala, Cameroon

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ABSTRACT

Background: Despite being a global pandemic, little is known about the factors influencing in-hospital mortality of COVID-19 patients in sub-Saharan Africa. This study aimed to provide data on in-hospital mortality among COVID-19 patients hospitalized in a single large center in Cameroon.
Methods: A hospital-based prospective follow-up was conducted from March 18 to June 30, 2020, including patients >18 years with positive PCR for SARS-COV-2 on nasopharyngeal swab admitted to the Laquintinie Douala hospital COVID unit. Predictors of in-hospital mortality were assessed using Kaplan Meir survival curves and Weibull regression for the accelerated time failure model. Statistical significance was considered as $p < 0.05$.
Results: Overall 712 patients (65,7% men) were included, mean age 52,80 ± 14,09 years. There were 580 (67,8% men) in-hospital patients. The median duration of hospital stay was eight days. The in-hospital mortality was 22.2%. Deceased patients compared to survivors were significantly older, had a higher temperature, respiratory rate, and heart rate, and lowest peripheral oxygen saturation at admission. After adjusting for age, sex, and other clinical patient characteristics, increased heart rate, increased temperature, decreased peripheral oxygen saturation. The critical clinical status was significantly associated with increased in-hospital mortality. In contrast, hospitalization duration greater than eight days and the use of hydroxychloroquine (HCQ) + azithromycin (AZM) therapy was associated with decreased risk of in-hospital mortality.
Conclusion: One in five hospitalized COVID-19 patients die in a low-middle income setting. Critical clinical status, dyspnea, and increased heart rate were predictors of in-hospital mortality. This study will serve as a prerequisite for more robust subsequent follow-up studies. Also, these results will aid in revising national guidelines for the management of COVID-19 in Cameroon.

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1. Introduction

The world is experiencing an unprecedented pandemic of coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in December 2019 in Wuhan, Hubei province, China. As of January 19, 2021, according to the World Health Organization (WHO) estimates, more than 96 million people have been infected worldwide, with more than 2000000 deaths [1]. Studies carried out in Europe, North America, and Asia seem to show that in a substantial minority of patients, COVID-19 can be severe, with particularly high fatality rates among older people (>65 years) and in those with certain common comorbid conditions, such as cardiovascular diseases (CVD), chronic pulmonary disease, chronic kidney disease (CKD), archaic genetic variants (in Eurasians), inborn errors or auto-antibodies interfering with interferon of immunity and cancer, but also cardiovascular risk factors (CVRFs) such as diabetes, hypertension, and obesity [2–6]. While the pathophysiology of COVID-19 remains incompletely understood, patients can develop severe acute respiratory distress syndrome (ARDS), but also shock, thrombosis, and multiple organ failure [2,3]. Mortality rates for patients admitted to intensive care units are as high as 22% [7], in China and 26% in Italy during the first wave [8].

Though there is an increased burden of several non-communicable diseases in sub-Saharan Africa (SSA) compared to other regions of the world, the African continent overall presents the lowest mortality rate, albeit this can be attributed to the low test per case ratio [9,10]. A large cohort study in South Africa (SA) suggests that risk factors such as gender, age, hypertension, diabetes, HIV, and tuberculosis were associated with COVID-19 outcome [11]. Furthermore, critical or severe COVID-19 and dyspnea on admission were potential predictors of mortality in the SSA setting [12]. Although a couple of studies have explored factors associated with COVID-19 mortality in SSA, few studies have reported the factors associated with in-hospital mortality in this setting. This study, therefore, seeks to provide more data on COVID-19 mortality with a focus on factors associated with in-hospital mortality among patients admitted at the Laquintinie Hospital, Douala, Cameroon.

2. Methods

2.1. Study design, study setting, and participants

We conducted a hospital-based cohort study at Laquintinie hospital in Douala; a university teaching hospital is a teaching hospital located in the heart of the city of Douala, the economic capital of Cameroon, with about 5 million inhabitants. This hospital is one of the three centers in the city of Douala approved by the Ministry of Public Health for COVID-19 patients and has an intensive care unit with a capacity of 12 beds. In this hospital, a triage system had been put in place, and only symptomatic COVID-19 (from mild to the critical clinical stage) patients were hospitalized per the national protocol. From March 18 to June 30, 2020, all consecutive consenting patients >18 years with a confirmed diagnosis of COVID-19 based on positive reverse transcriptase-polymerase chain reaction for SARS-COV-2 on a nasopharyngeal swab and hospitalized in Laquintinie hospital were included in this study. According to the Cameroon national protocol, every confirmed COVID receives treatment based on a combination of hydroxychloroquine (200 mg 3 times daily during 7 days and azithromycin 500 mg the first day and 250 mg from day 2 through 5). Patients with documented allergy with hydroxychloroquine or azithromycin received Lopinarivir-Ritonavir [12]. With the evolution of knowledge on this pathology, from May 1, 2020, the treatment has slightly evolved with the administration of anticoagulants (enoxaparin or rivaroxaban) and corticosteroids to all patients with saturation <93% and/or > 30% of lung involvement on computed tomography. The administration schedule for rivaroxaban was 15 mg twice daily while enoxaparin was given 1 IU/Kg/12 h. We used prednisolone 20 mg twice a day or methylprednisolone 40 mg/8 h IV in critically ill patients regarding corticoids.

This study was conducted following the declaration of Helsinki. Ethical clearance was obtained from the LHD institutional review board, whereas administrative clearance was obtained from the Regional Delegation of Public Health for the Littoral Region.

2.2. Data collection and definition

Patients' age, sex, comorbidities, smoking status, symptoms, vitals signs at admission, treatment received, and outcomes were collected from all patients. Variables were defined as follow: Heart rate/min (normal: 60–100, abnormal: < 60 & >100, Tachycardia >100); Respiratory rate/min (normal:12–20, abnormal <12 or >20); peripheral oxygen saturation (normal >96%, abnormal ≤96%); Temperature °C (normal: 36,5°–37,5°, abnormal: <36,5 °C or >37,5 °C, fever: ≥38 °C); Blood Pressure (BP) was measured according to the European Society of Cardiology Guidelines [13]. Clinical status (mild: mild clinical symptoms, no sign of pneumonia on imaging, Moderate: fever and respiratory symptoms (cough, dyspnea), with signs of pneumonia on imaging, Severe: respiratory distress with RR ≥ 30 cycles/min and/or SPO2≤ 93% at rest and/or PaO 2/FiO2≤ 300 mm Hg (1 mm Hg = 0.133 kPa), critical: respiratory distress enquiring mechanical ventilation and/or shock and/or failure of other organs and/or requiring admission to an intensive care unit (ICU). The primary outcome of interest was in-hospital all-cause mortality. Loss to follow up was considered when a patient left the hospital without medical consent.

2.3. Statistical analysis

R version 4.05 was used for statistical analysis. Baseline characteristics were compared by mortality status. Continuous variables are presented as mean and standard deviation for variables with a normal distribution and median with corresponding 25th and 75th percentile otherwise. Categorical variables are presented as frequencies and percentages. A chi-squared test was used for the comparison of categorical variables. Likewise, independent Student's T-test and Mann Whitney *U* test were used to compare normally distributed and skewed continuous variables accordingly. Kaplan Meier survival curves were plotted to compare survival probability based on clinical status. Due to violation of the assumptions for the Cox proportional hazard model, Weibull regression was used to create accelerated failure time regression models to estimate the crude and adjusted hazards ratio for in-hospital all-cause mortality. A p-value of <0.05 was considered for statistical significance.

3. Results

3.1. Demographic and clinical characteristics

Overall there were 712 patients (65,69% men) with laboratory-confirmed COVID-19, of which, 580 (67,8% men) were hospitalized and 132 (56,06% women) were followed as out-patients (Fig. 1). The mean age of hospitalized cases was 52.88(14.22) years. Survivors were younger than patients who died. Also, the prevalence of diabetes was significantly higher in patients who died.

In addition, deceased patients presented with higher body temperature, respiratory rate, and resting heart rate; similarly, deceased patients presented lower peripheral oxygen saturation at baseline. The most common clinical presentations were cough, fever, and dyspnea. Survivors were less likely to present with dyspnea.

The median duration of hospitalization was 8 days, and deceased patients had a shorter duration of hospital stay. The in-hospital all-cause mortality was 22.2% and was comparable between males and females. A linear trend of increasing mortality was observed from the lowest to the highest age quartile. Table 1 summarizes the baseline characteristics of study participants by mortality status.

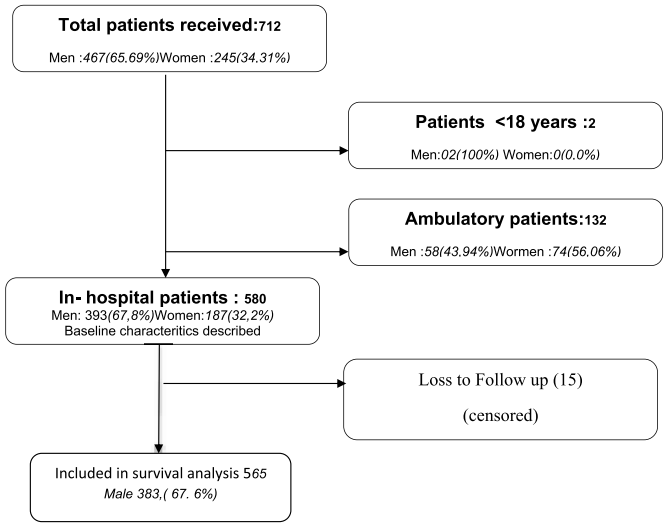

Fig. 1. Flow chart for study participants.

3.2. Factors associated with all-cause in-hospital mortality

There was an increased risk of mortality from mild through critical clinical status (log-rank < 0.01) (Fig. 2). For every 10 year increase in age, the risk of in-hospital mortality increased by 36%, and this effect was persistent in multivariable analysis (adjusted Hazards Ratio (1.28, [1.09–1.49], p < 0.01). Increased body temperature, heart rate, respiratory rate, and decreased peripheral oxygen saturation at baseline were associated with increased risk of in-hospital mortality. However, the increased respiratory rate was not significant after adjusting for age, sex, and other comorbidities. Dyspnea at baseline increased the crude risk of mortality by 767%; however, this was not significant in the multivariable analysis (aHR 2.09, [0.94–4.66], p = 0.07). Also, an increased risk of hospital mortality was observed across different clinical stages from mild to critical; however, this effect was consistent only for patients with critical clinical status at baseline. Admission to the intensive care unit during hospital stay increased mortality risk, although not significant after adjusting for other confounders. Duration of hospitalization more than eight days demonstrated a decreased risk in in-hospital mortality and was consistent in the univariable and multivariable models.

The combination of azithromycin and hydroxychloroquine decreased risk (aHR 0.19 [0.13–0.29], p= <0.001) of mortality by 81% percent and the effect of decreased mortality was consistent in multivariable analysis (aHR 0.57 [0.33–0.97], p = 0.04). The use of anticoagulants showed no significant effect on in-hospital mortality. Table 2 summarizes the results obtained from univariable and multivariable Weibull regression analysis.

4. Discussion

In this first large prospective observational study of hospitalized patients with COVID-19 in Cameroon, we found an in-hospital mortality rate of 22,2% due to the severe clinical status before admission. These results will be relevant in public health decision-making and in improving the care of COVID 19 patients in SSA [14]. Indeed, knowledge of these mortality figures could remind the population that this pathology is not benign and that preventive measures must continue to be applied. The mortality rates in hospitalized patients reported previously range from 4 to 28% [3,15–17] in developed countries and 29% in the SSA setting [12]. In the latter study, 56% of patients arrived in a critical condition, and 70% of deaths occurred within the first 24 h of admission, demonstrating the severity of the cases and probably the late arrival of patients at the hospital. In our study, 93% of the patients who died were in a severe or critical clinical status on arrival. In addition, the

Table 1
Baseline clinical characteristics of study participants.

Variables (Total)	Not Death n = 451	Death n = 129	Total n = 580	p-value
Age	51.35 (14.08)	58.23 (13.40)	52.88 (14.22)	<0.01
Age category (years)				
≤ 42	130(28.8)	17(13.2)	147(25.3)	<0.01
43 - ≤53	124(27.5)	25(19.4)	149(25.7)	
54 - ≤ 63	108(23.9)	45(34.9)	153(26.4)	
> 63	89(19.7)	42(32.6)	131(22.6)	
Gender (male)	301(66.7)	93(72.1)	394(67.9)	0.25
Medical History				
Alcohol – no.(%)				
Smoking (yes)	7(1.6)	5(3.9)	12(2.1)	0.1
Hypertension	152(33.7)	54(41.9)	206(35.5)	0.09
Obesity – no.(%)	55(12.2)	15(11.6)	70(12.1)	0.86
Diabetes– no.(%)	72(16.0)	35(27.1)	107(18.4)	<0.01
PreviousCVDs– no.(%)	130(28.8)	48(37.2)	178(30.7)	0.07
CKD	6(1.3)	3(2.3)	9(1.6)	0.42
Cancer	6(1.3)	0(0)	6(1)	0.19
HIV infection	18(4.0)	9(7.0)	27(4.7)	0.16
Clinical characteristics				
Cough	329(72.9)	91(70.5)	420(72.4)	0.59
Dyspnea	224(49.7)	120(93.0)	344(59.3)	<0.01
Chest pain	111(24.6)	36(27.9)	147(25.3)	0.45
Anosmia	37()	7	44	0.29
Dysguesia	54(12.0)	11(8.5)	65(11.2)	0.27
Diarrhea	51(11.3)	9(7.0)	60(10.3)	0.15
Nausea or voming	41(9.1)	7(5.4)	48(8.3)	0.18
Headaches	283(62.7)	84(65.1)	367(63.3)	0.62
Fever	301(66.7)	105(81.4)	406(70.0)	<0.01
Temperature (°C)	37.98	38.42 (0.99)	38.07 (0.94)	<0.01
Peripheral Oxygen saturation (%)	92.9(6.21)	78.45 (13.40)	89.8 (10.29)	<0.01
Resting heart rate	89.94 (15.06)	107.95 (21.43)	93.94 (18.28)	<0.01
Systolic blood pressure (mmHg)	137.95 (21.35	139.57 (27.1)	138.31 (22.90)	0.48
ICU hospitalization (yes)	63(13.9)	63(49.2)	126 (21.8)	<0.01
Duration of hospitalization (days)	9.0(7–11)	4.0(2–7)	8.0(5–11)	<0.01
Clinical status				
Mild	66(14.7)	2(1.6)	78(11.6)	0,115
Moderate	178(39.6)	6(4.8)	184(32.0)	0,891
Severe	164(36.4)	50(40.0)	214(37.2)	0,092
Critical	42(7.3)	67(53.6)	109(19.0)	0,222
Hydroxychloroquine + Azytromicyne	429(95.1)	93(72.7)	522(90.2)	<0.01
Use of steroids (yes)	126 (28.9)	42(32.6)	170(29.7)	0.49
Anticoagulants	249(55.6)	95(73.6)	344(59.6)	<0.01

CVD = cardiovascular disease, CKD = chronic kidney disease, ICU = intensive care unit.

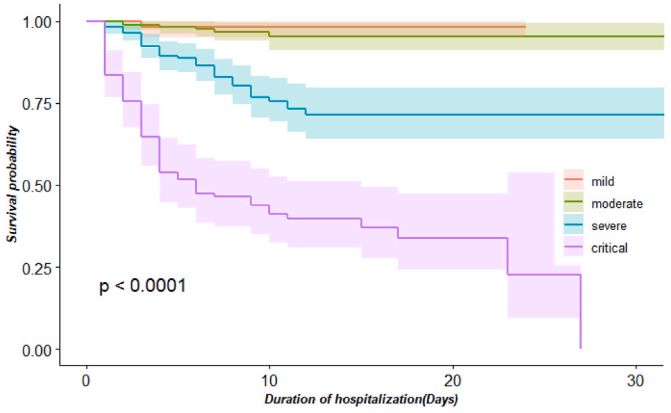

Fig. 2. Kaplan meier survival curve comparing survival probability across different clinical status at baseline.

Table 2
Factors predicting in-hospital mortality.

Variable	*Univariable analysis*			*Multivariable analysis*		
	Death	Crude HR	95% CI	aHR	95% CI	p-value
Age years (10-year increase)		1.36	1.19–1.55	1.28	1.09–1.49	<0.01
Gender (male)		1.07	0.72–1.58	0.89	0.58–1.37	0.59
Dyspnea (yes)		8.67	4.39–17.11	2.09	0.94–4.66	0.07
Body temperature (0.5 unit increase)		1.89	1.08–1.31	1.22	1.09–1.35	<0.01
Respiratory rate (4 unit increase)		1.51	1.42–1.62	1.10	0.99–1.23	0.08
Previous cardiovascular disease		1.15	0.79–1.66			
Diabetes (yes)		1.64	1.09–2.47	1.52	0.97–2.39	0.06
Hypertension (yes)		1.19	0.82–1.71	0.74	0.47–1.16	0.19
Peripheral Oxygen saturation (5 unit decrease)		1.52	1.44–1.62	1.17	1.07–1.29	<0.01
Heart rate (10 unit increase)		1.44	1.34–1.56	1.18	1.07–1.30	<0.01
Hospital stay (>8days)		0.07	0.04–0.11	0.04	0.02–0.07	<0.01
Clinical status(reference mild)						
Moderate		2.05	0.25–17.00	1.81	0.21–15.57	0.59
Severe		12.61	1.74–91.49	4.99	0.64–38.94	0.13
Critical		42.12	5.84–303.69	10.76	1.31–88.37	0.03
ICU admission (yes)		2.93	2.05–4.23	1.09	0.69–1.72	0.71
Azithromycin + Hydroxychloroquine combination		0.19	0.13–0.29	0.57	0.33–0.97	0.04
Steroid use		0.97	0.66–1.43			
Anticoagulant use		1.56	1.04–2.34	0.69	0.43–1.10	0.11

aHR = adjusted hazards ratio, ICU = intensive care unit.

presence of dyspnea and critical clinical state on admission were the main factors associated with in-hospital mortality. Although the ICU admission was not a factor associated with death after adjustment in the present study, these results show that it is important to treat patients early before they reach serious stages of the disease in our context where the hospital facilities are often insufficient to manage such patients [18]. Furthermore, the ICU mortality rate of 49% in our study remains higher than the average of 25.7% reported in the emerging literature [19].

This study identified diabetes as a factor associated with in-hospital mortality in the univariate analysis. On the contrary, other chronic conditions such as hypertension, obesity, smoking, chronic kidney disease, HIV infection, and cancer did not affect hospital mortality. In South Africa, for example, COVID-19 mortality was independently associated with HIV and tuberculosis infection [11] whereas, in Kinshasa, hypertension and diabetes emerged as a chronic conditions independently associated with hospital mortality [12].

Previously, older age has been reported as an important risk factor of death in COVID-19 disease. Our findings confirmed an increased risk of mortality for every 10-year increase in age. In developed countries, older age emerged as a strong mortality risk factor that can increase the risk by 30 fold for age groups over 80 years old [7,16,20]. In DRC, with a similar age pyramid, the non-survivors were older, and the risk of in-hospital death was increased [12]. Several clinical signs and symptoms such as dyspnea, increased temperature, increased heart rate, already described previously as risk factors for increased mortality, were found in our study. We also noted that prolonged duration of hospitalization was associated with a lower risk of in-hospital mortality; this can have implications on the number of hospital beds and equipment available to continue care of new cases of Covid 19 and thus indirectly worsening outcomes in emerging cases.

To date, there is no effective treatment for COVID-19. Still, the ICU mortality has decreased substantially over time, possibly due to better hospital case management, including better ventilation practices and potentially effective treatments [21]. Treatment regimens such as the association of hydroxychloroquine and azithromycin are extensively used in Africa despite controversies on the efficacity and cardiovascular safety [22,23].

The combination of hydroxychloroquine and azithromycin demonstrated a significantly reduced risk of in-hospital mortality in this study, similar to the reports in some studies [24]. However, these results have been contrasted by several studies [25–27]. This difference can be explained by the absence of randomization in our study. Also, it shall be noted that patients who received hydroxychloroquine and azithromycin combination were younger had higher peripheral oxygen saturation. Moreover, a relatively lower proportion of patients on hydroxychloroquine and azithromycin combination presented with a critical clinical status at baseline compared to their counterparts (16.7% vs. 41.5%)

Other medications such as corticosteroids and anticoagulants introduced in our treatment protocol six weeks after the beginning of this study did not impact hospital mortality in our study. However, the large randomized Recovery study has highlighted the benefits of glucocorticoids in the outcome of COVID-19 patients requiring oxygen. The lack of therapeutic efficacy of corticosteroids in our study could be explained by the delayed administration and the difference in the delivery modality in Cameroon.

Limitations

This study has several limitations: firstly, the single-center approach limits the generalization of our results. Secondly, the late arrival of patients in the hospital could increase the number of severe cases admitted and therefore overestimate the overall mortality in our series. Also, given COVID 19 is a new disease with emerging literature, most of the patients in our cohort could have been exposed to different treatment protocols throughout recruitment. Nevertheless, the substantial number of patients included in the present study and the scarcity of observational studies in our context makes this work useful for the scientific community.

CRediT authorship contribution statement

Marie Solange Ndom Ebongue: Conceptualization, writing, editing, Supervision, Software. **Daniel Lemogoum:** Conceptualization, writing, editing, Supervision. **Laurent Mireille Endale-Mangamba:** Data curation, Investigation. **Blaise Barche:** Methodology, Software, writing. **Christian Eyoum:** Data curation, Investigation. **Styve Hermane Simo Yomi:** Methodology, Software, writing. **David Mekolo:** Data curation, Investigation. **Vincent Ngambi:** Data curation, Investigation. **Jacques Doumbe:** Data curation, Investigation. **Christiane Medi Sike:** Data curation, Investigation. **Jerome Boombhi:** reviewing. **Grace Ngondi:** Data curation, Investigation. **Christian Biholong:** Data curation, Investigation. **Josephine Kamdem:** Data curation, Investigation. **Liliane Mbenoun:** Data curation, Investigation. **Calixthe Kuaté Tegeu:** Data curation, Investigation. **Armel Djomou:** Data curation, Investigation. **Anastase Dzudie:** reviewing, Supervision. **Felicité**

Kamdem: reviewing. **Ferdinand Ndom Ntock:** reviewing. **Liliane Kuaté Mfeukeu:** reviewing. **Eugène Sobngwi:** reviewing. **Ida Penda:** Supervision. **Richard Njock:** Supervision, reviewing. **Noel Essomba:** Supervision, reviewing. **Jean Cyr Yombi:** Reviewing. **William Ngatchou:** Conceptualization, writing, editing, Supervision, Software.

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