Vol. 24(1), pp. 1-12, January 2024
DOI: 10.5897/AJMHS2023.0250
Article Number: 074B74871680
ISSN 2384-5589

http://www.academicjournals.org/AJMHS

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African Journal of Medical and Health Sciences

Full Length Research Paper

Unveiling the hidden battle: Impact of Charlson comorbidities index on critical illness rate and mortality among hospitalized COVID-19 patients, comparing vaccinated and unvaccinated individuals in Kenya: A retrospective study

Isinta M. Elijah[1]*, W. Kitagwa[2], Dabo G Halake[3] and Youxin Wang[1,4]

[1]Beijing Key Laboratory of Clinical Epidemiology, School of Public Health, Capital Medical University, Beijing, 100069, China.
[2]Department of Public Health 2030-20200, School of Health Sciences Kericho, University of Kabianga, Kenya.
[3]Department of Environmental Health and Disease Control, School of Public Health, Jomo Kenyatta University of Agriculture and Technology, Nairobi 62000-00200, Kenya.
[4]Centre for Precision Medicine, Edith Cowan University, Perth 60127, Australia.

Received 11 July, 2023; Accepted 11 December, 2023

Fatal outcomes were observed in hospitalized COVID-19 patients, particularly among those who were unvaccinated and had comorbidities. Robust research is needed to validate these findings in both vaccinated and unvaccinated groups. The study, involving 1792 COVID-19 patients, explored the links between comorbidities and fatal outcomes. This single-center retrospective cohort study employed Cox proportional hazard regression to analyze the impact of comorbidities on COVID-19 fatalities, adjusting for age, sex, smoking and vaccination status. Males experienced severe illness (75%) or mortality (76.8%). Notably, most people admitted to the ICU were over 31 years old (96.2%), with individuals over 60 years old facing the highest fatality rate (61.6%). The proportion of ICU admissions increased with the Charlson Comorbidities Index (CCI), with CCI 1-3 at 51.0% and CCI >4 at 52.6%. Mortality linked to CCI was 55.4% for CCI 1-3 and 52.6% for CCI >4. The risk of ICU admission and mortality both increased with higher CCIs. Common comorbidities such as obesity, cardiovascular diseases, diabetes, chronic liver disease, chronic pulmonary obstructive disease, cancer/malignancy, chronic kidney disease and hypertension predicted critical illness and mortality among COVID-19 patients. The area under the receiver operating characteristic curve (AUC-ROC) for predicting critical illness was 0.90 (95% CI: 0.89-0.93), and for mortality, it was 0.90 (95% CI: 0.88-0.91). Additional factors, such as HIV and rheumatoid arthritis, independently predicted critical illness and mortality. The risk of critical illness and mortality showed an increase with the Charlson Comorbidities Index, both among vaccinated and unvaccinated individuals.

Key words: Charlson comorbidities index, Intensive care units (ICUs), mortality, vaccine.

INTRODUCTION

The global impact of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to escalate, with over 500 million people contracting coronavirus disease in 2019 (COVID-19) and more than 6.1 million reported deaths as of May 27, 2022. By the same date, a staggering 11.8 billion vaccine

doses had been administered worldwide (WHO, 2022a). In Africa, where over 9 million COVID-19 cases have been recorded since the onset of the pandemic, the death toll has reached 227,650. Despite these challenges, more than 180 million vaccinations have been administered across the continent, targeting a population of over 1.3 billion people, as of January 3, 2022 (WHO, 2021). In Kenya, as of April 24, 2022, the country had reported more than 324,000 COVID-19 cases and over 5,580 deaths. By December 31, 2021, Kenya had administered more than 10 million COVID-19 vaccine doses, with the majority of individuals receiving partial vaccination (Mwangi, 2021).

Globally, the disparities in mortality rates and the occurrence of late-stage critical illness have been observed. The factors contributing to these disparities include variations in clinical management practices, access to essential resources like vaccines, and differences in healthcare system standards across countries (Bennett et al., 2021). According to the American Centers for Disease Prevention and Control (CDC) and the World Health Organization (WHO), a significant number of individuals testing positive for COVID-19 ultimately survive the disease (WHO, 2021). WHO reports that about 80% of COVID-19 patients are either asymptomatic or experience mild illness based on available data (Bennett et al., 2021; Tessema and Nkengasong, 2021).

There is a growing body of evidence in ongoing research identifying predictors for an increased risk of hospitalization, critical illness and mortality from COVID-19. These predictors include advanced age, male gender and underlying conditions such as cardiovascular diseases, diabetes, malignancy/cancer, chronic kidney disease, hypertension, chronic liver disease, respiratory disease and dementia (Bennett et al., 2021; Shaikh et al., 2021). For instance, a recently published study in Ireland, involving 19,789 participants, highlighted that a BMI≥40 kg/m^2, chronic heart diseases, and male gender were associated with the risk of hospitalization, ICU admission, and mortality among COVID-19 patients (Bennett et al., 2021). The study further revealed that chronic kidney disease, neurological conditions, and malignancy/cancer had a significant association with higher mortality risks among COVID-19 patients (Bennett et al., 2021).

While numerous previous studies have linked comorbidities with fatal outcomes in COVID-19, most of these cohort studies have focused on unvaccinated hospitalized COVID-19 patients (Abhilash et al., 2022; Ayaz et al., 2020; Ge et al., 2021; T. Guo et al., 2020; Sadeghi et al., 2020; Surme et al., 2021). However, only a few studies have attempted to assess risk factors for severe outcomes among both vaccinated and unvaccinated hospitalized individuals. Unfortunately, evidence from the African population is lacking (Abhilash et al., 2022; Jere et al., 2000; Lopez Bernal et al., 2021; Thompson et al., 2021; Yadav et al., 2021; Yek et al., 2022). One significant limitation of studies lacking comparison between vaccinated and unvaccinated groups is that the identified risks may not be reliable due to the unadjusted influence of vaccination. Nevertheless, stratifying populations by vaccination status is essential to establish a reliable cause-and-effect relationship between comorbidities and fatal outcomes of COVID-19. Therefore, evidence from both the vaccinated and unvaccinated populations in this era of increased vaccination rates must provide comprehensive and robust insights into predictors of mortality and critical illness, contributing to the existing knowledge on the association between comorbidities and COVID-19 fatal outcomes.

Several cohort studies have reported the prevalence of comorbidities among COVID-19 patients, while other studies have reported an association between comorbidities and severe COVID-19 outcomes (Bennett et al., 2021; Fresán et al., 2021; Shaikh et al., 2021; Yek et al., 2022). However, the association between comorbidities and severe effects of COVID-19 (critical illness and mortality) among vaccinated and non-vaccinated COVID-19 patients is lacking to clearly show the impact of comorbidities among vaccinated and non-vaccinated COVID-19 patients. On the other hand, comorbidities have been reported to predict fatal outcomes among COVID-19 patients in various parts of the world (Albitar et al., 2020; Ge et al., 2021; L. Guo et al., 2020; Inciarte et al., 2020; Surme et al., 2021). However, understanding the severe intrinsic effects of COVID-19 among individuals with underlying comorbidities is challenging in this vaccine era. There are several dynamics in the confounding factors influencing the fatal outcomes of COVID-19; these confounding factors have changed since the world outbreak of COVID-19 and are likely to continue changing. The confounding includes the introduction of vaccines and therapeutics (Rosenberg et al., 2022), prevention and control public health strategies (Banholzer et al., 2021), and demographic factors (Venkatesan, 2020). Another confounder is the smoking status (Reddy et al., 2021). Any result on the association between comorbidities and fatal outcomes of COVID-19 without adjusting and controlling confounders can mislead the public and medical professionals on the actual effects of underlying comorbidities on the fatal outcome of COVID-19.

As of July 2021, only 2.3% of adult Kenyans had been vaccinated (MoH, 2021). Therefore, the study aimed to assess the association between comorbidities and fatal

*Corresponding author. E-mail: isintaelijah65@gmail.com. Tel: +254718683447.

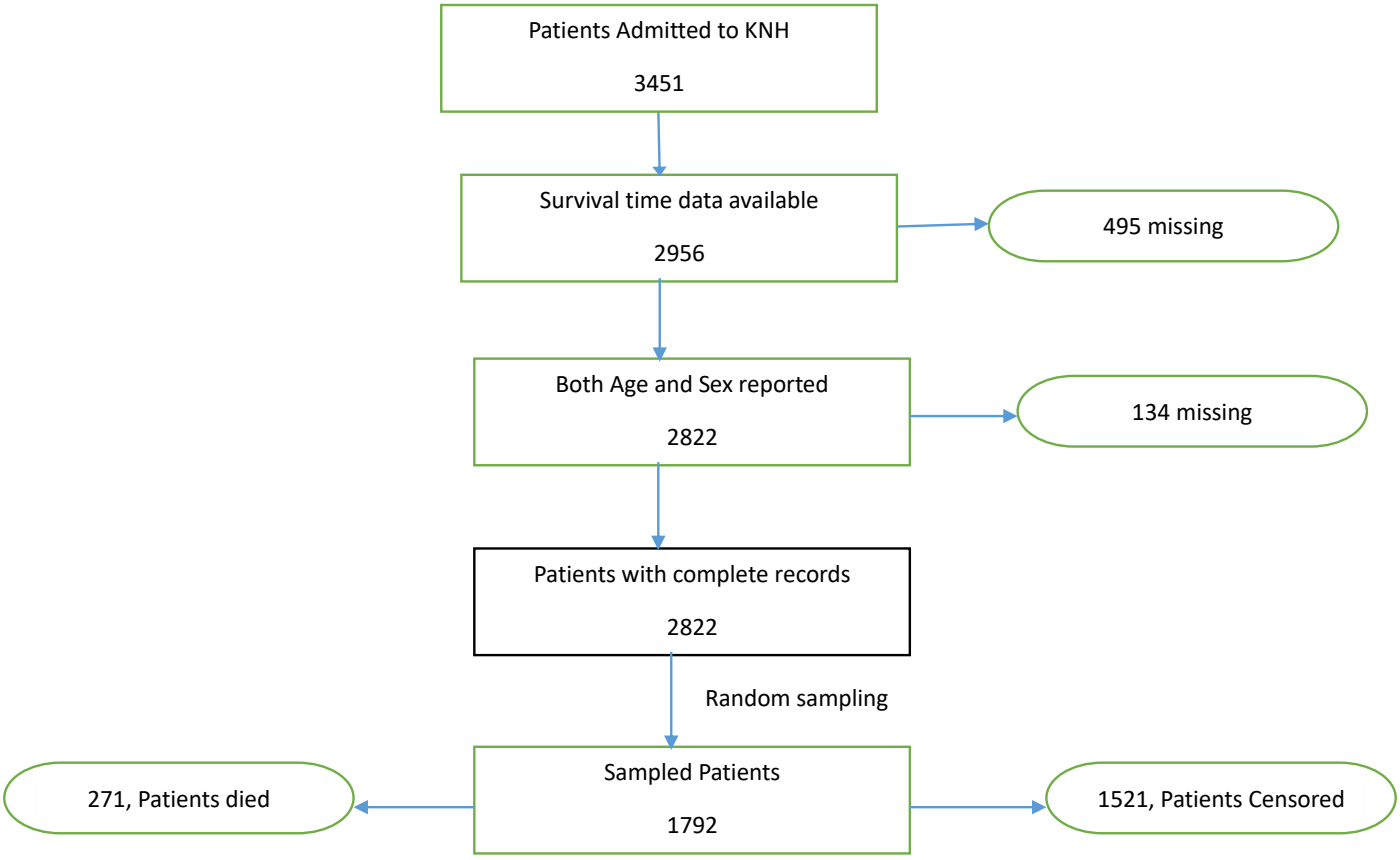

Figure 1. Flow chart for inclusion of patients in the final analysis.

outcomes of COVID-19 stratified by and adjusted for age, sex, smoking status and vaccination status among patients admitted to Kenyatta National Hospital.

MATERIALS AND METHODS

Study subjects

A hospital-based retrospective cohort study was conducted in Kenya where all COVID-19 (asymptomatic and symptomatic) cases were confirmed by RT-PCR laboratory test. The case that were admitted to Kenyatta National Hospital between 30th March 2021 and 30th December 2021 were included in the study. Any individual who met the laboratory SARS-CoV-2 detection criteria was a confirmed case. The testing guidelines in Kenya during the observation period were based on the requirements that those to be tested must have had any of the following: had COVID-19-like symptoms, the individual was a secondary index during contact tracing, or as part of mass testing programs aimed at control and prevention of the disease, had visited an affected area or region. Thus, the present study included all confirmed positive cases of SARS-CoV-2 using RT-PCR laboratory confirmatory test and admitted to Kenyatta National Hospital (KNH). Samples for laboratory diagnosis were collected through either oral-pharyngeal (OP) or nasal-pharyngeal (NP) swabs. Cases recruited in this study were those whose date of admission to KNH and date of change of status (died or discharged), alongside their age and sex, were reported. Patients with incomplete outcome information and vital baseline data and those transferred to other health institutions after admission were excluded from the study because of the challenge of getting their complete data. Out of 3,451 admitted patients, 2,956 patients' survival time data was available, out of which 2,822 reported gender and sex. Finally, 1,792 participants were randomly sampled from 2,822 patients with complete record data (Figure 1).

The primary outcomes of this study are ICU admission and mortality; ICU admitted case is defined as a patient admitted to the ICU for any given period, while mortality is defined as the death of a patient after laboratory-confirmed COVID-19 positive result within 30 days. Vaccination history was captured during admission to classify patients according to vaccination status. Since the patients could not recall the type of vaccine and number of doses they had received in this present study, the patients who received one or more doses of any vaccine at least two weeks before the onset of symptoms were considered vaccinated, while the rest were considered unvaccinated.

Underlying comorbidities were identified based on the international classification of disease diagnostic codes (ICD) 11th version (WHO, 2022b). Most identified comorbidities have been validated in different chart reviews and data algorithms and demonstrated high sensitivity and specificity (Chen et al., 2017; Mondor et al., 2018). The comorbidities include asthma (ICD-11 CA23.3), obesity (ICD-11 5B81.Z), cardiovascular diseases (including Ischemic acute stroke (ICD-11 8B11.5Z), Ischemic cardiac disease (ICD-11 BA5Z), hemorrhagic stroke (ICD-11 8B00.Z) and congestive heart failure (ICD-11 BD10)), malignancy/cancer (ICD-11 2D4Z), chronic kidney disease (ICD-11 GB61.Z), hypertension (ICD-11 BA00.Z), chronic

liver disease (ICD-11 DB99.0), chronic pulmonary obstructive disease (ICD-11 CA22.Z), dementia (ICD-11 6D8Z), diabetes (ICD-11 5A14), human immunodeficiency virus (ICD-11 1C62.Z) and rheumatoid arthritis (ICD-11 FA20.Z).

Data collection procedure

Data were extracted analytically from hospital medical records using a modified WHO COVID-19 case investigation form (WHO, 2020b). Patient-level information collected included sex (male or female), age in years, duration of hospitalization, and days spent in the ICU. Vaccination status was recorded as either vaccinated or not vaccinated, coded as yes/no. The presence of underlying comorbidities was noted as present or absent (yes/no) for individuals with at least one or more underlying comorbidities. The recorded comorbidities included cardiovascular diseases (CVDs), hypertension, diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), chronic liver disease, HIV, cancer/malignancy, dementia and rheumatoid arthritis. Morbid obesity was recorded as present or absent, defined as BMI≥30 kg/m^2, and coded as yes/no for the obese and non-obese, respectively. Smoking history data was collected and defined as smokers (former or current smokers) or non-smokers, coded as yes/no, respectively.

Statistical analysis

Descriptive analysis was conducted, continuous data were tested for normality using the Kolmogorov-Smirnov test, and it was then presented as mean ± standard deviation (SD). The categorical variables for sex, vaccination status, and underlying comorbidities were presented as frequencies and relative frequencies, and cross-tabulation using the chi-square test was used to analyze the difference in variables between ICU admission and non-ICU admission and also between survivors and non-survivors. Survivors and non-survivors for continuous data discriminant analysis were conducted to discriminate between ICU and non-ICU admission.

The Charlson comorbidity index was used to determine the number and severity of comorbid conditions (CCI). The CCI was modified and used in this study. The CCI in its modified form was used (Quan et al., 2005). The CCI is a weighted score that includes 17 comorbid illnesses such as congestive heart failure (weight 1), myocardial infarction (weight 1), chronic lung disease (weight 1), cerebrovascular disease (weight 1), hemiplegia or paraplegia (weight 2), dementia (weight 1), diabetes without problems (weight 1), diabetes with complications (weight 2), malignancy (weight 2), and solid metastatic tumor (weight 6). CCI was divided into three categories for the multivariable analysis: 0, 1-3 and ≥4 because CCI may be a proxy measure for the patient's overall status.

A multivariate Cox regression model examined the association between comorbidities and critical illness (ICU admission). Adjusted hazard ratio (aHR) was measured at a 95% confidence interval (CI) and reported with the p-value for each variable. To minimize biases from confounding factors when assessing the association between comorbidities and severe outcomes of COVID-19, the data was stratified by age, sex, vaccination status and smoking status. Different methods control confounding factors in retrospective cohort studies, including stratification (Zhang et al., 2017), multivariate regression analysis (Alexopoulos, 2010), and propensity matching score methods (Austin, 2011). Therefore, stratification and multivariate regression adjusted for age, sex, vaccination status and smoking status was chosen.

A multivariate Cox proportional hazard regression model stratified by and adjusted for age, sex, smoking status, and vaccination status examined the association between comorbidities and mortality outcomes during sensitivity analysis.

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows IBM version 26.1. All p values reported in the study were deemed statistically significant if $p<0.05$ and were all two-tailed.

Ethical approval

The Commission waived the requirement for informed consent in agreement with the Helsinki Declaration of 1976 since the study entirely depended on secondary data. The Institutional Ethical Review Committee approved this study of the University of Kabianga, approval number IERC/2021/009, and Capital Medical University in Beijing, China, approval number No. 2020SY23. Kenya National Commission for Science, Technology and Innovation sought the official research permit, license number NACOSTI/21/8553. To access hospital data, official permission and approval were sought from the Hospital Research and Ethical Approval Board of the University of Nairobi with P184/03/2021.

RESULTS

Demographic statistics

The general baseline characteristics of the 1792 COVID-19 patients admitted to Kenyatta National Hospital (KNH) in Kenya are presented in Table 1 across the COVID-19 outcomes (ICU admission and mortality). The majority of those admitted to the ICU, 262 (75.7%), were male, while 208 (76.8%) out of 271 non-survivors were also male. Most ICU admissions were above 31 years of age. However, most non-survivors were aged >60 years 167 (61.6%). Among ICU admissions, 21 (6.1%) were smokers; on the other hand, 35 (12.9%) were smokers among non-survivors. Patients with at least one COVID-19 vaccine were predominantly fewer than 80 (23.1%) among those admitted to ICU compared to those not admitted 242 (69.9%). Additionally, most of those vaccinated against COVID-19 survived 239 (74.2%) compared to those who died 83 (27.8%). The proportion of those admitted to ICU increased with an increase in the number of comorbidities, CCI 1-3, 80 (51.0%) and CCI >4, 41 (52.6%). Similarly, the number of those who died was proportionately high in CCI 1-3, 87 (55.4%) and CCI>4, 41(52.6%). The comorbidities with COVID-19 outcomes are as follows; out of 27 cases of obesity, 18 (66.7%) were admitted to ICU, and 20 (74.1%) died; out of 111 patients with CVDs, 62 (55.9%) were admitted to ICU, and 86 (77.5%) died from COVID-19. On the other hand, 21 (29.6%) of HIV cases were admitted to ICU, while 15 (21.1%) died from COVID-19. 68 (70.1%) diabetic cases were admitted to ICU, while 82 (84.5%) died. In total, 21 (56.8%) of patients with CLD were admitted to ICU, while 22 (59.4%) died. Among those with COPD, 35 (70.0%) required ICU admission, while 46 (92.0%) died. In COVID-19 patients with malignancy/cancer, 21 (65.6%) required ICU admission, and 31(96.9%) died. For those with chronic CKD, 11 (34.4%) were admitted to ICU, and 13 (40.6%) died. Out of 66 hypertension patients with COVID-19, 37 (56.1%) required ICU admission, while 46 (69.7%) died. On the other hand, 7 (58.0%) patients with dementia required

Table 1. Distribution of confounders and comorbidities with COVID-19 outcomes of ICU admission and mortality among COVID-19 patients.

Risk factor	ICU admission status				Mortality status			
	Admitted (n%)	Not admitted (n%)	aHR(95% CI)	P-value	Non-survivors (n%)	Survivors (n%)	aHR(95% CI)	P-value
Male	262(75.7)	875(60.5)	1.79(1.39-2.30)	<0.0001	208(76.8)	928(61.1)	1.79(1.33-2.40)	<0.0001
Age (years)								
0-30	13(3.8)	256(17.7)	1		8(3.0)	261(17.2)	1	0.277
31-60	169(48.8)	973(67.3)	1.53(0.86-2.71)	0.144	96(35.4)	1046(68.8)	1.50(-0.72-3.12)	<0.0001
>60	164(47.4)	217(15.0)	3.06(1.71-5.46)	<0.0001	167(61.6)	214(14.1)	4.40(2.11-9.14)	
Smoking	21(6.1)	36(2.5)	1.85(1.17-2.90)	0.008	35(12.9)	22(1.4)	3.66(2.52-5.31)	<0.0001
Vaccination	80(23.1)	242(16.7)	1.37(1.01-1.85)	0.042	83(30.6)	239(15.7)	1.46(1.06-2.00)	0.022
CCI								
0	225(14.5)	1332(85.5)	1		143(9.2)	1414(90.8)	1	
1-3	80(51.0)	77(49.0)	2.52(1.89-3.35)	<0.0001	87(55.4)	70(44.6)	4.43(3.27-5.00)	<0.0001
≥4	41(52.6)	37(47.4)	3.76(2.65-5.33)	<0.0001	41(52.6)	37(47.4)	5.04(3.51-7.23)	<0.0001
Obesity	18(5.2)	9(0.6)	1.30(0.77-2.19)	0.326	20(7.4)	7(0.5)	1.53(0.94-2.51)	0.091
CVDs	62(17.9)	49(3.4)	2.63(1.85-3.76)	<0.0001	86(31.7)	25(1.6)	3.59(2.59-4.98)	<0.0001
HIV	21(6.1)	50(3.5)	1.06(0.55-2.02)	0.870	15(5.5)	56(3.7)	1.14(0.58-2.26)	0.700
Diabetes	68(19.7)	29(2.0)	2.18(1.58-2.99)	<0.0001	82(30.3)	15(1.0)	2.65(-1.94-3.62)	<0.0001
Chronic liver disease	21(6.1)	16(1.1)	0.73(0.38-1.40)	0.338	22(8.1)	15(1.0)	0.58(0.29-1.14)	0.113
COPD	35(10.1)	15(1.0)	4.24(2.86-6.29)	<0.0001	46(17.0)	4(0.3)	4.86(3.34-7.08)	<0.0001
Cancer/malignancy	21(6.1)	11(0.8)	0.97(0.54-1.73)	0.904	31(11.4)	1(0.1)	2.11(1.25-3.57)	0.005
CKD	11(3.2)	21(1.5)	2.07(0.99-4.33)	0.054	13(4.8)	19(1.3)	1.67(0.82-3.41)	0.159
Hypertension	37(10.7)	29(2.0)	2.46(1.39-4.37)	0.002	46(17.0)	20(1.3)	2.74(1.56-4.82)	<0.0001
Dementia	7(2.0)	5(0.3)	0.65(0.28-1.50)	0.310	7(2.6)	5(0.3)	0.44(0.18-105)	0.063
Rheumatoid arthritis	8(2.3)	12(0.8)	1.07(0.46-2.46)	0.883	10(3.7)	10(0.7)	0.74(0.34-1.60)	0.440

aHR (95% CI): Adjusted Hazard Ratio at 95% confidence interval for predictors of ICU admission and mortality adjusted for all listed independent variables. CI, confidence interval; CCI, Charlson comorbidity index; CVDs, cardiovascular diseases; HIV, human immunodeficiency virus; COPD, chronic pulmonary obstructive disease; CKD, chronic kidney disease.

ICU admission, and 7 (58.0%) died, and in inclusion, 8 (40.0%) patients with rheumatoid arthritis were admitted to ICU, while 10 (50.0%) died.

The association between comorbidities and critical illness among COVID-19 patients

The data presentation of the association between comorbidities tested in this study and the risk of ICU admission among hospitalized COVID-19 patients was recorded (Table 2). After adjusting for sex, age, smoking 0.0001]. The risk of ICU admission significantly increased among COVID-19 patients with obesity [aHR: 7.27, 95% CI: 2.87-18.42, *P*<0.0001], CVDs [aHR: 3.51, 95% CI: 2.27-5.43, *P*<0.0001], HIV [aHR: 2.02, 95% CI: 1.13-3.60, *P*=0.017], diabetes [aHR: 6.84, 95% CI: 4.22-11.10, *P*<0.0001], CLD [aHR: 4.10, 95% CI: 1.97-8.53, *P* <0.0001], COPD[aHR: 7.71, 955 CI: 4.00-14.85, *P*<0.0001] cancer/malignancy [aHR: 7.37, 95% CI: 3.40-16.00, *P*<0.0001], CKD [aHR: 2.43,95% CI: 1.09-5.39, p=0.029], and hypertension [aHR: 4.78, 95% CI: 2.75- 8.31, *P*<0.0001]. There was no significant association between those with dementia [aHR: 3.07, 95% CI: 0.87-10.85, *P*=0.082], rheumatoid arthritis [aHR: 2.56, 95% CI: 0.96-6.83, *P*=0.062] and risk of ICU admission (Table 2).

Table 2. Association of comorbidities with ICU admission and mortality among COVID-19 patients multivariate Cox regression analysis.

Comorbidity	ICU admission				Mortality			
	cHR (95% CI)	p-value	aHR (95% CI)	p-value	cHR (95% CI)	p-value	aHR (95% CI)	p-value
CCI								
0								
1-3	2.56(1.98-3.31)	<0.0001	2.52(1.89-3.35)	<0.0001	5.17(3.95-6.76)	<0.0001	4.43(3.27-6.00)	<0.0001
≥4	4.33(3.10-6.04)	<0.0001	3.76(2.65-5.33)	<0.0001	6.30(4.45-8.92)	<0.0001	5.04(3.51-7.23)	<0.0001
Obesity	8.76(3.90-19.68)	<0.0001	7.27(2.87-18.42)	<0.0001	4.90(3.10-7.73)	<0.0001	3.51(2.21-5.56)	<0.0001
CVDs	6.2294.19-9.25)	<0.0001	3.51(2.27-5.43)	<0.0001	8.05(6.22-10.43)	<0.0001	4.13(3.08-5.54)	<0.0001
HIV	1.80(1.07-3.05)	0.027	2.02(1.13-3.60)	0.017	1.40(0.83-2.36)	0.207	1.45(0.85-2.48)	0.170
Diabetes	11.95(7.60-18.81)	<0.0001	6.84(4.22-11.10)	<0.0001	8.38(6.46-10.88)	<0.0001	4.41(3.34-5.82)	<0.0001
CLD	5.78(2.98-11.19)	<0.0001	4.10(1.97-8.53)	<0.0001	4.64(3.00-7.18)	<0.0001	2.77(1.76-4.33)	<0.0001
COPD	10.74(4.00-14.85)	<0.0001	7.71(4.00-14.85)	<0.0001	7.81(5.68-10.74)	<0.0001	5.24(3.78-7.28)	<0.0001
Cancer	8.43(4.02-17.66)	<0.0001	7.37(3.40-16.00)	<0.0001	4.68(3.20-6.84)	<0.0001	4.27(2.90-6.29)	<0.0001
CKD	2.23(1.06-4.660	0.034	2.43(1.09-5.39)	0.029	3.78(2.16-6.61)	<0.0001	4.79(2.71-8.45)	<0.0001
Hypertension	5.85(3.54-9.66)	<0.0001	4.78(2.75-8.31)	<0.0001	7.16(5.20-9.85)	<0.0001	5.27(3.78-7.36)	<0.0001
Dementia	5.95(1.88-18.87)	0.002	3.07(0.87-10.85)	0.082	3.68(1.73-7.81)	0.001	1.65(0.77-3.53)	0.199
Rheumatoid arthritis	2.83(1.15-6.97)	0.024	2.56(0.96-6.83)	0.062	5.3992.85-10.18)	<0.0001	4.33(2.27-8.27)	<0.0001

cHR (95% CI), crude hazard ratio at 95% confidence interval; aHR(95% CI), adjusted hazard ratio at 95% confidence interval adjusted for sex, age, smoking status and vaccination status.

The association between comorbidities and risk of mortality among COVID-19 patients

Table 2 also shows the association between comorbidities and risk of in-hospital mortality among confirmed cases of COVID-19 admitted to KNH (n=1792). The Cox regression model successfully identified the association between comorbidities and mortality (Figure 2). After adjusting for sex, age, smoking status and vaccination status, the mortality risk increased with the number of comorbidities; sicker patients with CCI 1-3 and ≥4 comorbidities were more likely to die than those without comorbidities (CCI 1-3[aHR: 4.43, 95% CI: 3.27-6.00, *P*<0.0001], CCI ≥4 [aHR: 5.94, 95% CI: 3.51-7.23, *P*< 0.0001]). The risk of mortality from COVID-19 significantly increased among COVID-19 patients with obesity [aHR: 3.51, 95% CI: 2.21-5.56, *P*<0.0001], CVDs [aHR: 4.13, 95% CI: 3.08-5.54, *P*<0.0001], diabetes [aHR: 4.41, 95% CI: 3.34-5.82, *P*<0.0001], CLD [aHR: 2.77,95% CI: 1.76-4.33, *P*<0.0001], COPD[aHR: 5.24, 955 CI: 3.78-7.28, *P*<0.0001] cancer/malignancy [aHR: 4.27, 95% CI: 2.90-6.29, *P*<0.0001], CKD [aHR: 4.79,95% CI: 2.71-8.45, *P*<0.0001], hypertension [aHR: 5.27, 95% CI: 3.78-7.36, *P*<0.0001], and rheumatoid arthritis [aHR: 4.33, 95% CI: 2.27-8.27, *P*<0.0001]. However, in all these comorbidities, the risk was higher in unvaccinated patients than in the vaccinated. There was no significant association between those with HIV [aHR: 1.45, 95% CI: 0.85-2.48, *P*=0.170], dementia [aHR: 1.65, 95% CI: 0.77-3.53, *P*=0.199] and risk of mortality (Table 2).

Table 3 presents sensitivity analysis results for the association of the Charlson comorbidity index with COVID-19 outcome of ICU admission stratified by age, sex, vaccination status and smoking status. The final Cox regression model results stratified by age, sex, vaccination status and smoking status strata are represented in Table 3. The results indicate an increased risk of ICU admission with increased CCI; sicker patients with CCI 1-3 and ≥4 were more likely to be admitted to ICU than those without comorbidities. Sicker patients with CCI 1-3 were 2.42, 2.56, 2.56 and 2.51 times more likely to be admitted to ICU than those without comorbidities. On the other hand, those with

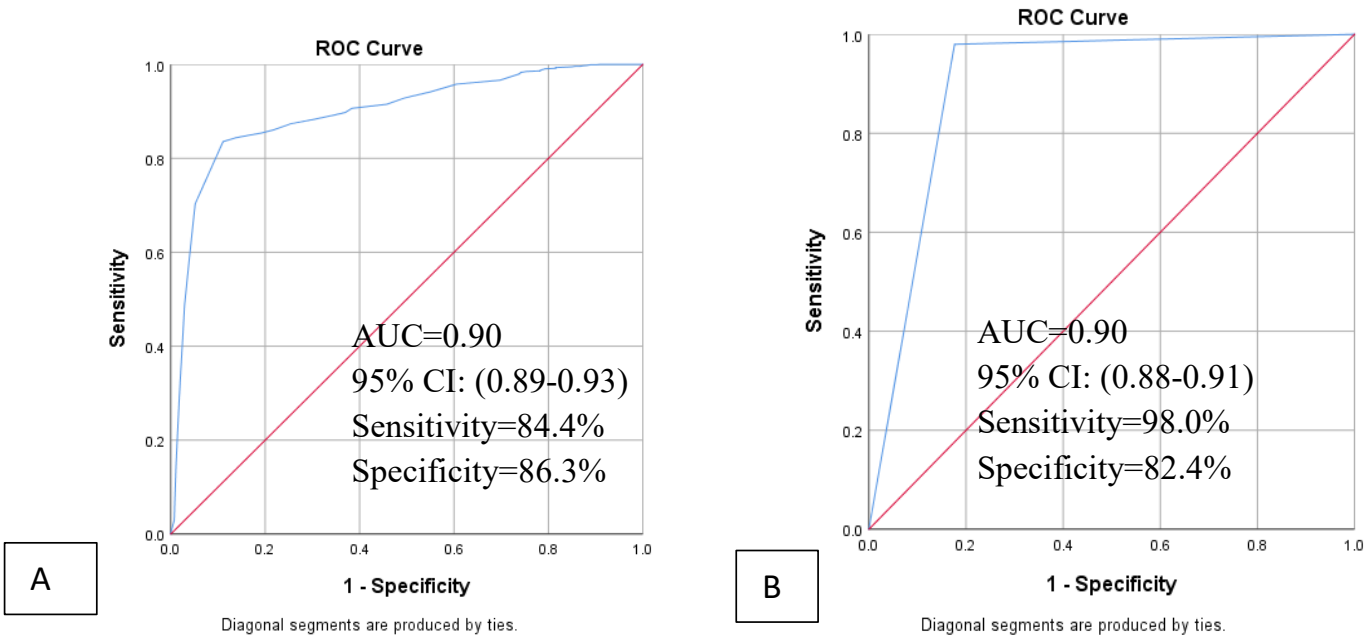

Figure 2. Receiver operating characteristic (ROC) curve analysis of Cox regression model to determine association of comorbidities and ICU (A) admission and mortality (B) among COVID-19 patients.

CCI> 4 were also 3.75, 3.61, 3.84 and 3.77 times more likely to be admitted to ICU than those without comorbidities. COVID-19 patients with obesity, CVDs, HIV, diabetes, CLD, COPD, cancer, CKD, hypertension, and rheumatoid arthritis had an increased risk of ICU admission p<0.05 (Table 3).

Table 4 presents the sensitivity analysis result for the association of the Charlson comorbidity index with COVID-19 outcome stratified by age, sex, vaccination status and smoking status. The final Cox regression model results stratified by sex, age, smoking status and vaccination status strata are represented in Table 4. The results indicate that the risk of mortality increases with the number of comorbidities; that is, sicker patients with CCI 1-3 and ≥4 comorbidities are more likely to die than those without comorbidities. Sicker patients with CCI 1-3 were 4.33, 4.28, 4.48 and 4.46 times more likely to die than those without comorbidities stratified by age, sex, vaccination status and smoking status, respectively. On the other hand, those with CCI> 4 were also 4.94, 5.02, 5.05 and 5.00 times more likely than those without comorbidities. COVID-19 patients with obesity, CVDs, diabetes, CLD, COPD, cancer, CKD, hypertension, and rheumatoid arthritis had an increased risk of mortality p<0.05 (Table 4).

DISCUSSION

This single-centered retrospective study recruited 1,792 confirmed COVID-19 cases, among which the study identified the risk of ICU admission and in-hospital mortality among COVID-19 patients. This is the first study with the largest sample size to explore the association between comorbidities and fatal outcomes of COVID-19 (ICU admission and mortality) among vaccinated and unvaccinated hospitalized COVID-19 patients in Kenya, Africa. Previous studies have associated the severe outcome of COVID-19 with age, sex, smoking and other clinical parameters (SPO2 levels, oxygen support, and health status) (Medina et al., 2020; Rahman et al., 2021; Ramanathan et al., 2020). In this study, age, sex, smoking status and vaccination status were adjusted for and thus not included in the multivariate analysis results.

After sensitivity analysis, the key findings in this present study indicate that the risk of mortality and critical illness rate increase as the Charlson comorbidities index (CCI) increases among vaccinated and unvaccinated patients. Critical illness and mortality risks significantly increased among individuals with comorbidities than individuals without comorbidities. Previous studies have indicated that vaccination protects against COVID-19 variants from fatal outcomes in people with underlying conditions (Chandrashekar et al., 2022; Cook and Roberts, 2021; Rosenberg et al., 2022). A study on the vaccine's effectiveness showed at least one shot of the vaccine prevents fatal outcomes of the disease (Behera et al., 2022). Even after primary vaccination, a sizable fraction of the population may be at risk, necessitating extra efforts to avoid severe COVID-19 consequences. This study gives strong evidence that even though there is a COVID-19 vaccine breakthrough, individuals with

Table 3. Stratified Cox regression by age, sex, vaccination status and smoking status for the association between Charlson comorbidity index and ICU admission.

Comorbidity	Stratified by age		Stratified by sex		Vaccination status stratified		Smoking status stratified	
	aHR[a](95% CI)	*P*-value	aHR[b](95% CI)	*P*-value	aHR[c](95% CI)	*P*-value	aHR[d](95% CI)	*P*-value
CCI								
0	1		1		1		1	
1-3	2.42(1.82-3.22)	<0.0001	2.56(1.92-3.42)	<0.0001	2.56(1.93-3.41)	<0.0001	2.51(1.89-3.35)	<0.0001
≥4	3.75(2.65-5.32)	<0.0001	3.61(2.55-5.10)	<0.0001	3.84(2.71-5.44)	<0.0001	3.77(2.66-5.34)	<0.0001
Obesity	2.40(1.48-3.90)	<0.0001	2.60(1.60-4.22)	<0.0001	2.49(1.54-4.04)	<0.0001	2.55(1.58-4.13)	<0.0001
CVDs	3.08(2.24-4.22)	<0.0001	3.24(2.37-4.43)	<0.0001	3.23(2.35-4.42)	<0.0001	3.25(2.38-4.44)	<0.0001
HIV	1.68(1.06-2.66)	0.026	1.56(0.98-2.46)	0.059	1.69(1.07-2.67)	0.024	1.64(1.04-2.59)	0.033
Diabetes	3.40(2.57-4.50)	<0.0001	3.84(2.90-5.08)	<0.0001	3.62(2.73-4.80)	<0.0001	3.71(2.81-4.90)	<0.0001
CLD	2.27(1.44-3.56)	<0.0001	2.26(1.44-3.56)	<0.0001	2.37(1.50-3.73)	<0.0001	2.38(1.52-3.75)	<0.0001
COPD	3.98(2.76-5.73)	<0.0001	4.32(3.00-6.22)	<0.0001	4.18(2.90-6.03)	<0.0001	4.26(2.96-6.14)	<0.0001
Cancer	1.46(0.93-2.29)	0.103	1.71(1.08-2.69)	0.021	1.63(1.04-2.56)	0.032	1.59(1.01-2.49)	0.043
CKD	4.27(2.32-7.86)	<0.0001	4.42(2.40-8.14)	<0.0001	4.14(2.24-7.63)	<0.0001	4.37(2.37-8.05)	<0.0001
Hypertension	4.04(2.84-5.76)	<0.0001	4.10(2.88-5.85)	<0.0001	4.21(2.95-6.02)	<0.0001	4.28(3.00-6.09)	<0.0001
Dementia	1.44(0.67-3.08)	0.355	1.42(0.66-3.06)	0.364	1.53(0.71-3.30)	0.277	1.45(0.68-3.12)	0.337
Rheumatoid arthritis	5.57(2.70-11.46)	<0.0001	5.65(2.74-11.66)	<0.0001	4.84(2.34-10.04)	<0.0001	5.33(2.59-11.00)	<0.0001

aHR[a] adjusted hazard ratio for sex, vaccination status and smoking status, aHR[b] adjusted hazard ratio for age, vaccination status and smoking status, aHR[c] adjusted hazard ratio for age, sex and smoking status, aHR[d] adjusted hazard ratio for age, sex and vaccination status.

underlying comorbidities are at increased risk of the severe outcome of the disease. Even though this result gives strong evidence of an increased association between comorbidities and severe outcomes from COVID-19 stratified by vaccination status, it should be consciously interpreted because the vaccinated individuals were not classified as not fully vaccinated, partially vaccinated, and unvaccinated due to a lack of adequate complete data on vaccination status. Developing countries with fragile health systems are expected to have inadequate medical records.

The present study has revealed that CCI predicts mortality and critical illness from COVID-19. The findings are consistent with the study conducted in England and Wales, which indicated that patients who died from COVID-19 had an average of 2.2 comorbidities across the ages (Cook and Roberts, 2021). Thus, the findings and the findings from England and Wales affirm that risk group prioritization should be selected based on the severity of comorbidities rather than the number (Campbell and Caul, 2020). However, the findings from England and Wales were from only unvaccinated COVID-19 patients, unlike the present findings from both vaccinated and unvaccinated individuals. This study observed that obesity, cardiovascular diseases, hypertension, diabetes, COPD and cancer/malignancy were the most prevalent underlying comorbidities among those who required ICU admission and failed to survive. In this current study, obesity, CVDs, diabetes, chronic liver disease, COPD, cancer/malignancy, chronic kidney disease and hypertension were associated with an increased risk of ICU admission and mortality. These findings also reflect the European Centre for Disease Prevention and Control (ECDC) surveillance report, highlighting diabetes, cardiac disorders, and cancer/malignancy as the most prevalent three comorbidities among severe COVID-19 cases (ECDC, 2021). Also, these findings agree with a systematic review and meta-analysis published recently in China (Zhou et al., 2020). The present study further observed obesity was associated with an increased risk of ICU admission. The findings support previous findings that associated

Table 4. Stratified Cox regression by age, sex, vaccination status, and smoking status for the association between Charlson comorbidity index and COVID-19 mortality.

Comorbidity	Stratified by age		Stratified by sex		Stratified by vaccination		Stratified by smoking	
	aHR[a](95% CI)	*P*-value	aHR[b](95% CI)	*P*-value	aHR[c](95% CI)	*P*-value	aHR[d](95% CI)	*P*-value
CCI								
0	1		1		1		1	
1-3	4.33(3.20-5.88)	<0.0001	4.28(3.15-5.81)	<0.0001	4.48(3.30-6.07)	<0.0001	4.46(3.29-6.04)	<0.0001
≥4	4.94(3.44-7.10)	<0.0001	5.02(3.50-7.21)	<0.0001	5.05(3.52-7.26)	<0.0001	5.00(3.48-7.18)	<0.0001
Obesity	3.22(2.03-5.10)	<0.0001	3.47(2.18-5.52)	<0.0001	3.54(2.23-5.62)	<0.0001	3.45(2.18-5.48)	<0.0001
CVDs	4.03(3.00-5.41)	<0.0001	4.07(3.03-5.46)	<0.0001	4.14(3.08-5.55)	<0.0001	4.17(3.11-5.59)	<0.0001
HIV	1.45(0.85-2.46)	0.177	1.50(0.88-2.56)	0.137	1.44(0.84-2.45)	0.184	1.44(0.85-2.46)	0.177
Diabetes	4.24(3.21-5.59)	<0.0001	4.51(3.41-5.96)	<0.0001	4.56(3.46-6.06)	<0.0001	4.39(3.32-5.79)	<0.0001
Chronic liver disease	2.75(1.75-4.31)	<0.0001	2.71(1.73-4.25)	<0.0001	2.76(1.76-4.34)	<0.0001	2.73(1.74-4.28)	<0.0001
COPD	5.23(3.76-7.28)	<0.0001	5.16(3.71-7.17)	<0.0001	5.28(3.80-7.34)	<0.0001	5.17(3.72-7.18)	<0.0001
Cancer/malignancy	4.13(2.80-6.10)	<0.0001	4.07(2.75-6.03)	<0.0001	4.32(2.93-6.37)	<0.0001	4.22(2.86-6.22)	<0.0001
CKD	4.65(2.64-8.21)	<0.0001	4.82(2.73-8.51)	<0.0001	4.87(2.75-8.61)	<0.0001	4.84(2.74-8.54)	<0.0001
Hypertension	5.24(3.75-7.32)	<0.0001	5.32(3.81-7.44)	<0.0001	5.28(3.77-7.38)	<0.0001	5.25(3.76-7.33)	<0.0001
Dementia	1.64(0.77-3.51)	0.204	1.60(0.75-3.43)	0.225	1.62(0.75-3.47)	0.219	1.64(0.77-3.52)	0.201
Rheumatoid arthritis	4.45(2.33-8.49)	<0.0001	4.47(2.34-8.55)	<0.0001	4.42(2.31-8.45)	<0.0001	4.25(2.23-8.13)	<0.0001

aHR[a] adjusted hazard ratio for sex, vaccination status and smoking status, aHR[b] adjusted hazard ratio for age, vaccination status and smoking status, aHR[c] adjusted hazard ratio for age, sex and smoking status, aHR[d] adjusted hazard ratio for age, sex and vaccination status.

obesity with an increased risk of poor prognostic outcomes among COVID-19 (Bennett et al., 2021; Shaikh et al., 2021).

In this study, obesity, CVDs, COPD, diabetes, chronic liver disease, cancer/malignancy, chronic kidney disease, hypertension, and rheumatoid arthritis were independently associated with mortality among COVID-19 patients. However, their mortality risks increased with the number of comorbidities. This result agrees with a study conducted in the United States that although individuals with comorbidities are still vaccinated, there is an increased risk of hospitalization and severe outcome from COVID-19 (Yek et al., 2022). Therefore, even though individuals with underlying comorbidities get vaccinated, they still require particular interventions such as chronic disease management, preventing this group from exposure to deadly variants, more vaccine booster doses, and proper pharmaceutical therapy to prevent severe COVID-19 outcomes (Yek et al., 2022).

Although there are conflicting findings regarding the effects of HIV on COVID-19 (Inciarte et al., 2020; Tesoriero et al., 2021), the present findings indicated a significant increase in the risk of critical illness. Still, there was no significant influence of HIV on the mortality risk among COVID-19 patients. No known pathophysiology can explain the findings. However, evidence has indicated that immunocompromised people living with HIV with low CD4 cell count, and not on ART have an increased risk of critical illness from COVID-19 (Liz Essley Whyte, 2020; WHO, 2020a). In the present study, most hospitalized patients were male, and in Kenya, according to KDHS, 85.3% of men among people living with HIV are on ART. Another reason could be that most HIV individuals in this study were young hence less risk of other comorbidities, common in advanced age (Yek et al., 2022). The reasons are not exclusive and satisfactory; therefore, a more exclusive study should be conducted to validate the present finding in Kenya, which is among the countries with a high prevalence of HIV globally, and determine a causal relationship.

The strength of this study is that it is the first study to examine the association of comorbidities with severe COVID-19 outcomes among vaccinated and unvaccinated populations in Kenya, with the largest sample size. Second,

Kenya has a high burden of the prevalence of cardiovascular conditions, cancer, diabetes, and HIV (MoH-Kenya, 2015). Therefore, validating the association between these comorbidities and severe outcomes from COVID-19 benefits the public and the government. Although the likelihood of Severe COVID-19 outcomes is lowered in vaccinated persons with comorbidities as recorded in other studies (Bell et al., 2022; Whittaker et al., 2022), the present study still has revealed that whether vaccinated or not, individuals who are immunocompromised or have other underlying illnesses are at increased risk. To lower the likelihood of catastrophic COVID-19 outcomes, these individuals should receive targeted interventions such as chronic disease management precautions to reduce exposure, immunization, booster vaccine doses, and effective pharmacological therapy. It is expanding COVID-19 immunization coverage that may reduce risk.

Another strength of this study is that the extensive data was extracted from a national hospital that admits individuals from diverse populations. Additionally, the data used in the study were extracted from the hospital with the most prominent COVID-19 recorded cases in Nairobi County, one of the most affected counties in Kenya. Therefore, this allows the present study's findings on ICU admission and mortality to be compared with other counties in Kenya that were not highly affected by COVID-19.

Nevertheless, there are several limitations in the current study; first, data was collected retrospectively; hence bias might have been encountered. Second, estimation bias might have occurred due to missing data in some variables, thus reducing the sample's representativeness. Third, data were collected when the vaccination threshold had not reached even 10% of the Kenyan population, thus affecting vaccination status interaction estimates. Fourth, the vaccination status could not be classified as complete, partial, indeterminate, or unvaccinated due to a lack of an adequate record of vaccination status. Lastly, the study did not collect laboratory findings due to incomplete records, and thus this study might have omitted essential confounders such as biomarkers. Given that it is essential to acknowledge all the limitations, it is also crucial to note that our present study was not intended to evaluate causal effects.

Conclusion

The risk of critical illness and mortality increases with the number of comorbidities; sicker patients with CCI 1-3 and ≥4 comorbidities were more likely to die than those without underlying conditions. Results stratified by vaccination status indicated that both vaccinated and unvaccinated individuals with comorbidities are at an increased risk of severe COVID-19 outcomes compared to their healthy counterparts. Hence, special prevention measures, such as additional vaccine boosters, are still required to protect this vulnerable group from COVID-19 infection and its severity.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

ACKNOWLEDGMENT

The authors express gratitude for the funding provided by the Beijing Talent Project (2020A17). They would also like to extend their appreciation to Tychicus Ogoti for editing the manuscript and Peterson Maranga for conducting data analysis and providing technical advice. Furthermore, the authors are thankful to the administration of Kenyatta National Hospital for granting access to and allowing the extraction of data. Approval for this work was obtained from the institutional ethics committees of the following universities: Capital Medical University in Beijing, China; the University of Kabianga in Kericho, Kenya; and the University of Nairobi, Kenya.

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