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COLLEGE OF MEDICINE & HEALTH SCIENCES
SCHOOL OF MEDICINE & PHARMACY

MEMOIR

FEATURES AND OUTCOME OF PATIENTS WITH SEVERE AND CRITICAL COVID-19: A RETROSPECTIVE CROSS-SECTIONAL ANALYTICAL STUDY

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Submitted in Partial Fulfillment of the requirements for the Award of a Degree in Master of Medicine Science in Anesthesiology of University of Rwanda

In the

College of Medicine and Health Sciences

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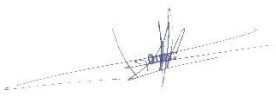
DECLARATION

I, GASHAME Dona Fabiola, declare that this proposal is my original work and has never been presented for a degree award or any other award in any University.

This dissertation is presented for the award of a Degree in Master of Medicine Science in Anesthesiology.

GASHAME Dona Fabiola

Sign  Date: 09/09/2022

Supervisor: Prof Theogene TWAGIRUMUGABE, M.D, Mmed, FCCM, PhD

Sign  Date: 09/09/2022

DEDICATION

I most gratefully dedicate this work to the Almighty God who stayed alongside through my life.

I strongly dedicate this to my family for their encouragement and their sacrifice during my studies.

To my research supervisor, all my classmates for the best moments bonded together, finally to all my relatives and friends.

God bless you

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Appreciations to my supervisor for his valuable guidance in this project. I am also indebted to my brothers, friends and family for their valuable support and encouragement.

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Thanks to the Almighty God, the creator who has made every accomplishment to happen, to Him the glory belongs forever and ever.

Thank you to all.

Abstract

Background: Clinical spectrum of COVID-19 disease passes from symptom free or with mild upper respiratory symptoms to the acute respiratory distress syndrome (ARDS). The virus may affect different organs. Risk factors to progression to the severe forms of the diseases have been described as an urgent research priority. The case mix and outcome of these patients have not been analyzed and published to guide the scientific community on this new pandemic. Data are badly lacking from Low Income Countries, in general and in Rwanda, in particular.

Aim: The aim was to determine the main clinical features and outcome of severe and critical COVID-19 patients during the third wave of the pandemic at the University Teaching Hospital of Butare (CHUB), Rwanda.

Methods: This was a retrospective study design. Subjects were patients with confirmed SARS-CoV-2 by PCR and/or Ag RDT, hospitalized for care in ICU/HDU for COVID-19 at CHUB from May to October 2021. Data including demographic characteristics, clinical symptoms, vaccination status, comorbidity, inflammatory markers, therapeutic support modalities and other specific treatment for COVID-19, antibiotherapy, discharge status and hospital length of stay were collected from the patients' medical records. Categorical data were presented in terms of frequency and percentage while continuous data were presented as median (IQR)). Logistic regression (binary and multivariate logistic regression analysis) were used to study the relationship between the outcome (mortality) and possible predictors. A $p<0.05$ was considered as statistically significant.

Results: 98 patients were taken on in this study and median (IQR) of their age was 63.5(51-75). The median (IQR) of LOS in days was 6(3-10) and the most frequent comorbidity was hypertension present in 24.5% of cases. 72.45% presented with cough, 66% presented with shortness of breath and 31.6% with chest pain, eighteen patients (18.37%) presented with decreased level of consciousness. The most common complications were respiratory failure at rate of 64.3% including ARDS cases (21.4%), Acute Kidney Injury (AKI) at rate of 19.4% and septic shock at rate of 9.1%. More than a half (61.2%) of patients admitted with severe or/ and critical COVID-19 disease died and almost all deaths were COVID-19-related. The multivariable logistic regression showed that increased urea and UVA score at admission were independent factors for in-hospital mortality.

Conclusion: There was a high mortality for severe and critical COVID-19 patients admitted at CHUB. This mortality could have been predicted by high urea (AKI) and UVA score.

Key words: COVID-19, Clinical features, risk factors, mortality and outcome.

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LIST OF ACRONYMS AND ABBREVIATIONS

Ag-RDT: Antigen detection rapid diagnostic test

AKI: Acute Kidney Injury

ARDS: Acute Respiratory Distress Syndrome

CDC: Centre of Disease Control

CHUB: Centre Hospitalier Universitaire de Butare

CI: Confidence Interval

CMHS: College of Medicine and Health Sciences

HDU: High Independent Unit

ICU: Intensive Care Unit

ICUs: Intensive Care Units

IQR: Inter-quartile range

IRB: Institutional Review Board

LICs: Low Income Countries

LOS: length Of Stay

OR: Odd ratio

PCR: Polymerase Chain Reaction

qSOFA: Quick Sequential Organ Failure Assessment

Ref: Reference

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

SOFA: Sequential Organ Failure Assessment

SPSS: Statistical Package for Social Sciences

UVA: Universal Vital Assessment

UR: University of Rwanda

CHAPTER I: INTRODUCTION

1.1 Background

Coronavirus disease 2019 (COVID-19) results from the coronavirus 2(SARS-CoV-2) infection(1). A novel coronavirus that caused unprecedented outbreak that started in China, has rapidly expanded to the entire globe causing a public health emergency. The clinical spectrum of COVID-19 disease passes from symptom-free or with mild upper respiratory symptoms to the acute respiratory distress syndrome (ARDS). Moreover, the virus may affect different organs and systems with mainly the respiratory, cardiovascular and hematological systems being most severely affected. Risk factors to progression to the severe forms of the diseases have been described as an urgent research priority (2).

The primal case of COVID-19 disease was discovered in China, late 2019 and by 19 December, 273 million patients and 5.3 million deaths had been reported worldwide. The presentation of COVID-19 is variable; symptoms vary from symptom-free to lethal. The majority suffer from cough or shortness of breath , fatigue, headache, and sometimes fever (3), fever is crucial but not the entirely symptom of infection (4).

The prevalence of respiratory failure in COVID-19 patients is around 20%, other reports revealed that around 25% were admitted to an Intensive Care Unit (ICU)(5).

The mortality rate in severe and critical COVID-19 is high in general and rises amidst elderly. Early medical management is essential to decrease the mortality of severe or/ and critical patients. Hence, it is important to screen those with a high risk of complications including death at admission. Nevertheless, this is especially difficult due to restrained medical resources and staff and the substantial number of patients(6).

Rwanda initially admitted all patients infected with COVID-19 irrespective of the disease's severity. However this practice changed with the rapidly increasing number of cases during the third wave. With adoption of Home-Based care, only severe and critical cases were admitted to the ICUs and refurbished for the purpose. Centre Hospitalier Universitaire de Butare (CHUB) was selected to serve the South and Western part of the country to provide care for severe cases in ICU and or High Dependent Unit (HDU).

The case mix and outcome of these patients have not been analyzed and published to guide the scientific community on this new pandemic in such context.

This study aimed to evaluate the clinical presentation and outcome of patients with severe and critical COVID-19.

1.1. Problem statement.

On the basis of the 10th International Committee on Taxonomy of Viruses (ICTV) report, two human coronaviruses under the genus *Alphacoronavirus* and subgenus *Duvinacovirus*, coronavirus 229E and under the genus *Betacoronavirus*, subgenus *Embecovirus* HCoV-OC43, give rise to upper respiratory tract infections. On the report of previous studies, coronavirus is normally associated with low mortality rate and in rare case results in critical illness(4).

A formerly nomogram proposed five factors for prognosticating the outcome: "Acute Physiology and Chronic Health Evaluation II (APACHE II), creatine kinase (CK), C-reactive protein (CRP), immunoglobulin A (IgA), and the interaction between CK and APACHE II". Inflammation markers upon admission are an errorless biomarker for mortality predilection in COVID-19 patients. Yet, risk factors associated with poor prognosis are uncertain(6).

Also the symptoms and comorbidities which forcibly predicts the disease severity and outcome are indeterminate. Undertaking this study, the main objective was to provide demographic, clinical and biological characteristics that may be associated with poor outcome of the disease in severe and critical COVID-19 patients hospitalized at CHUB.

1.2. Objectives of the study

1.2.1. Main Objective

To evaluate clinical manifestations and outcome of severe and critical COVID-19 patients at CHUB during the third wave of the pandemic in Rwanda.

1.2.2. Specific objectives

To characterize severe and critical COVID-19 patients admitted at CHUB during the third wave of the pandemic in Rwanda.

To describe the main clinical features of severe and critical COVID-19 infection during the third wave of the pandemic in Rwanda.

To determine the length of stay (LOS) of patients with severe and critical COVID-19 during the third wave of the pandemic in ICU and HDU.

To determine the hospital mortality rate associated with severe and critical COVID-19 and independent factors.

To identify independent factors associated with in-hospital mortality for this group of patients at CHUB ICU/HDU

1.3. Research questions

What are the demographic characteristics of severe and critical COVID -19 patients during the third wave of the pandemic?

What are the main clinical manifestations of severe and critical COVID-19 during the third wave of the pandemic?

What is LOS in ICU/HDU patients with severe and critical COVID-19 during the third wave of the pandemic?

What is the hospital mortality rate of patients with severe and Critical COVID-19 during the third wave of the pandemic?

What are the independent factors associated with poor prognosis?

1.5. Operation definition

For the purpose of this study and based on Center for Disease Control (CDC) guidelines of COVID- 19 management, Severe and critical COVID-19 is defined as positive virologic test associated with any of signs or symptoms of COVID-19 (7).

Table 1: Criteria for diagnosis of Severe or Critical COVID-19 (8)

"Patients with SpO2<94% on room air at sea level"
"A ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2 /FiO2) <300 mm Hg or SpO2/FiO2 ≤ 315"
"A respiratory rate >30 cycle per min",
"Lung infiltrates >50%"
"Critical Illness*:* Individuals with respiratory failure, septic shock, and/or multiple organ dysfunction".

CHAP II: LITERATURE REVIEW

We conducted a search of literary writings using the main web based scientific journals and the keywords: “COVID-19”, “2019-nCov”, “coronavirus and SARS-CoV-2”, “clinical features”, “Mortality”, “Outcome”.

2.1. Theoretical literature review

The worldwide COVID-19 pandemic has expanded, affecting practically all countries, and the primal case was identified in December 2019 in China(9). COVID-19 disease is caused by the infection of the acute respiratory syndrome coronavirus 2(SARS-CoV-2).

This type of virus has an intermediate host and is then transmitted to humans(10), via (i) direct contact once a person gets contact with one’s with respiratory symptoms or even asymptomatic, and via (ii)indirect contact with areas and items used on the infected person(8).

Since the primal case was discovered in 2019, and by December 2021, 272 million infected persons and 5.3 million deaths have been reported worldwide(3). The first case in Africa was reported in Egypt in February, 2020. In Rwanda, the first case arrived in March, 2020(10) and from March to June 2022, 130 278 cases of COVID-19 with 1459 deaths were reported to World Health Organization (WHO). On 29 May 2022, a total of 22 214 312 vaccine doses have been delivered(11).

The majority of severe cases are from people aged over 60 years and in those with underlying conditions, like cardiovascular diseases, cerebro-vascular diseases and diabetes. (12). However, age , cardiovascular diseases, CKD, chronic lung disease, diabetes, pregnancy and obesity constitute the most important risk factors for severe COVID-19 (7).

The incubation period for COVID-19 is 14days from the time of being exposed, with incubation period of 4 to 5days(7). The commonest symptoms of COVID-19 infection are cough, shortness of breath, fatigue and fever. Others signs include gastrointestinal symptoms, headache and chest tightness(4).Patients may suffer from variable clinical manifestations from symptom-free to severe and critical illness.

Case definitions may vary by regions also have evolved over time according to epidemiological situations. WHO has established case definitions. Suspect patient is the one “with any acute

febrile illness, any sign/symptom of respiratory disease or flu-like illness, a new loss of smell and taste sensations, headache, myalgia, abdominal pain, nausea and/or vomiting and decreased level of consciousness"(8) and "with no other etiology that explains the clinical manifestations" and "with a history of travel or residence in area reporting local or community transmission in the course of the 14 days prior to symptom onset"(13) or "a patient for whom the imaging of the lungs is carrying suggestion of COVID-19 pneumonia but the laboratory test is still pending"(8). Probable case is a "suspect case for whom testing for the COVID-19 is reported as presumptive OR a suspect case for whom testing could not be performed for any reason OR a suspect case for whom the imaging of the lungs is suggestive of COVID-19 pneumonia but the laboratory test is negative"(8). Confirmed case is a "person (dead or alive) with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms"(8).

Commonest laboratory findings include low white cells count. Other biochemical findings include elevated levels of liver enzymes , C-reactive protein (CRP), D-dimer, ferritin and lactate dehydrogenase (LDH)(14). Patients admitted in ICU had more laboratory abnormalities set side by side with non ICU patients(12), procalcitonin level is generally normal in early phases, but it increases in patients requiring ICU care(13).

Radiology findings may vary with patients age, progression of the disease, immune status, comorbidity, and first medical intervention(12), Chest X-Ray (CXR) findings are not specific, and early phases of the disease findings can be normal. The commonest features include lobar or multi-lobar or bilateral consolidations(13), COVID-19 patients manifested classic features on Computed Tomography (CT) of "bilateral multilobar ground glass opacities along with peripheral or posterior distribution"(15).

The COVID-19 testing detects sequences of virus RNA by NAAT and antigen test with viral cultures confirmation if necessary(8).

No therapies or antiviral drug against infection caused by SARS-CoV-2 have proven to be effective , however some therapeutics showed benefits in some subgroups of patients or for particular end points depending on severity of illness(15). At the moment, the therapeutic strategies are only supportive. Prevention is directed at lowering transmission in the community(13). Oxygen therapy, antibiotics for bacterial superinfections (12), coping with organs injuries, control of complications and comorbidities, nutritional support and mental health

interventions(16). No antiviral drug showed to work in COVID-19 disease in humans(13), however it has been used combined with empirical antibiotic treatment to treat COVID-19 patients(12). The monoclonal antibody products showed to decrease the risk of being hospitalized and death in mild to moderate COVID-19 patients and those with risk factors for disease worsening(8). The corticosteroids use in COVID-19 is unclear and controversial. Studies done on corticosteroids use in COVID-19 disease found no effect on the outcome (17). On the other hand, the dexamethasone administration showed to improve outcome in patients requiring respiratory support (18).

Prevention is made by isolation of COVID-19 disease patients and personal protective equipment (PPE) for health-care providers(17). COVID-19 vaccination decrease the rate of disease worsening and help in reducing the spread and rate of infection(19).

2.2 Empirical literature review

The clinical manifestations of COVID-19 disease vary from symptom-free to mild, moderate, severe or critical. Even though mild cases are most frequent, severe and critical patients also exist (20). Severe COVID-19 disease is described as "severe pneumonia with clinical signs, such as fever, cough, dyspnea, fast breathing with any the following: respiratory rate>30 breaths/min; or SpO2< 94% on room air at sea level or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg or SpO2/FiO2≤315 mmHg, or lung infiltrates >50%". Critical COVID-19 is described as " respiratory failure, septic shock, and /or Multiorgan dysfunction"(7).

Increased age is involved in severe COVID-19 and the predisposing factors for COVID-19 tend to be elderly and comorbidities (i.e, cardiovascular diseases, cerebrovascular diseases, diabetes, renal diseases, respiratory diseases….)(20). Most of severe and critical COVID-19 patients are men, and a large number presented with multiple comorbidities(1).Dyspnea and shortness of breath are the commonest clinical manifestations of severe disease and in patients with fever, the risk of developing severe COVID-19 disease is high(21) and commonest comorbidities are hypertension, diabetes mellitus and heart disease(22). The most common laboratory abnormalities seen are low albumin level, increased D-Dimer, elevated LDH, low platelets, high levels of high-sensitivity cardiac troponin I, creatinine kinase, alanine and aspartate aminotransferase, urea and creatinine(20). The commonest CT findings were ground glass

opacities, consolidation, crazy-paving pattern, and spider web sign. Compared with other patients, the severe and/or critical COVID-19 patients have poor prognosis and high mortality(23). Age, low white cells count, respiratory rate≥ 30/min are independent risk factors associated with poor prognosis(6).

CHAPTER III: METHODOLOY

3.1. Research design and approach

This was a retrospective study design incorporating patients with laboratory-confirmed SARS-CoV-2 by PCR or Ag RDT, admitted for care to the ICU/HDU for COVID-19 at CHUB from May- October 2021.

3.2. Research setting

This study was conducted at CHUB which is located in Butare City within Huye district, catchment area of around 4 million inhabitants living in Southern and a part of the Western Provinces, and Referral hospitals for 14 DH and PH.

3.3. Population

This study was made up by all adult patients admitted for severe or/and critical COVID-19 disease at CHUB in ICU/HDU during the third wave of the pandemic.

3.4. Sampling

All patients hospitalized in HDU/ICU during the third wave with COVID-19 diagnosis were eligible to be included in this study.

3.5. Sampling strategy

Inclusion criteria

All patients admitted for severe and critical COVID-19 disease in ICU/HDU from May to October 2021.

Exclusion criteria

-Patients without sufficient records in the file e.g Vital signs at admission, baseline investigations, and files without precision on the outcome.

- Pediatric patients

- Mild to moderate COVID-19 infection

3.6. Data Collection instruments

Data collection tool for this study using a questionnaire composed of social demographics characteristics and clinical characteristics of the participants was used. Social demographics characteristics include patient age, body mass index, gender, marital status and province. Clinical characteristics included signs and symptoms, medical history and medications, comorbidity (i.e., hypertension, diabetes, ischemic heart disease with troponin levels >0.03ng/, cancer, CKD, immunosuppression, and liver disease), vital signs, lab investigations on admission, imaging , anti-COVID-19 pharmacological therapy (antimalarial, antivirals, monoclonal antibodies), respiratory support intervention (oxygen high flow therapy, invasive mechanical ventilation (IMV) or noninvasive mechanical ventilation (NIV)), renal replacement therapy, nutrition support (enteral and total parenteral nutrition (TPN)), complications, and outcome.

3.7. Procedure of Data collection

The primary investigator collected the data after obtention of the Institutional Review Board (IRB) approval of College of Medicine and Health Sciences (CMHS) and Research Ethic Committee of CHUB. The data collected included social demographic characteristics as mentioned on the tool. Clinical characteristics included signs and symptoms, comorbidity, medications history, vital signs within 24hrs of admission, imaging, lab investigations on admission, anti-COVID-19 pharmacological therapy, respiratory support intervention, renal replacement therapy, nutrition support, complications (i.e. Respiratory failure, ARDS diagnosed as stated by Kigali modification of Berlin definition, Acute kidney injury (AKI)…), and outcome(i.e., ICU LOS, death, heart failure, de novo diabetes mellitus, DVT/PE,…).

3.8. Data analysis

Epidata version 3.1 for database was created by entering the collected data, afterwards exported to SPSS version 25 for analysis. Descriptive data are presented in this way : categorical data are presented using frequency and percentage and continuous data are outlined by median values with their interquartile ranges (IQR) as they were skewed in their distribution and their distribution was tested using Shapiro-Wilk test and logistic regression (binary and multivariable logistic regression analysis) were used to study the correlation between the outcome (mortality) and possible predictors namely age, gender, marital status, qSOFA, hypertension and diabetes mellitus. Variables with a strong association ($p<0.25$) were used in a multivariable logistic

regression to identify the independent factors linked to the outcome of severe and Critical COVID-19. The difference in median values of numeric predictors of mortality was tested using Mann Whitney U test. A $p<0.05$ was considered as statistically significant.

3.9. Ethical considerations

The primary investigator submitted the study protocol to IRB/CMHS and Research Ethic Committee of CHUB to get ethical approvals. Using code on each questionnaire anonymity was ensured while confidentiality was ensured using a safe and closed store. The soft data collected and saved on the computer is protected by a strong password.

3.10. Data management

Hard data is secured in a locked cabinet while soft data is kept in the computer and on a drive protected with a strong password. Data will be kept for five years and all files will be deleted or incinerated.

3.11. Data dissemination

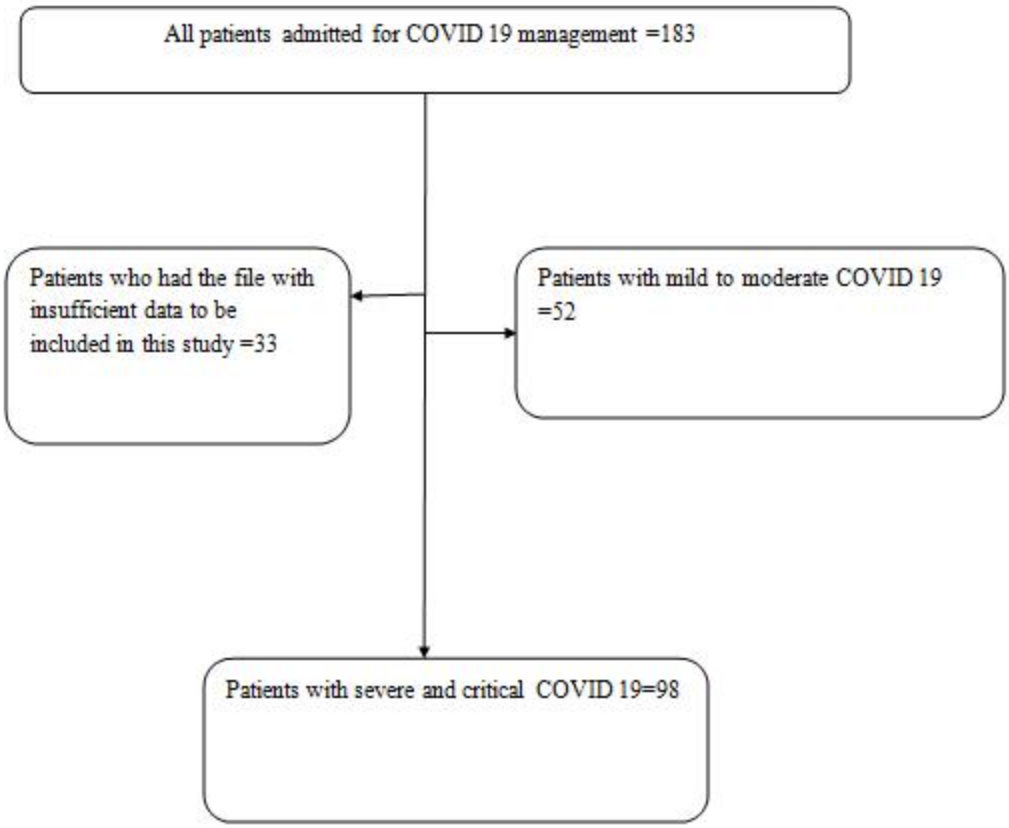
Findings of this study will be published and made accessible to anyone. The final project will be printed and submitted to the CMHS library for public use.

3.12. Limitations and challenges

Due to the nature of a retrospective study, some data were not available for evaluation, such as labs that were not completed during admission, vaccination status …

CHAP IV.RESULTS

Figure 1: Patient flow chart



In total we enrolled 183 patients admitted for COVID-19 management. 52 patients were not included from the study because they were mild to moderate COVID-19 cases while the study concerned severe and critical cases. Others 33 patients were not considered for inclusion because the insufficient data in their files

Table 2: Description of all study subjects

Characteristics	n	%
Age in years		
Median (Q1-Q3)	63.5 (51-75)	
Age groups		
≤35	10	10.20
36-65	43	43.88
>65	45	45.92
Gender		
Male	42	42.86
Female	56	57.14
Marital status		
Married	90	91.84
Single	8	8.16
Comorbidities		
Hypertension	24	24.49
Diabetes mellitus	17	17.35
Liver disease	4	4.08
Vaccination status		
vaccinated with 1st dose	2	2.04
Not vaccinated	7	7.14
Not documented	89	90.82
Time between symptoms and consultation in hours		
Median (Q1-Q3)	168 (96-198)	

The median age was 63.5 years and 57% were females and the majority (91.8%) was married. 24.5% had hypertension and 17.3% had diabetes mellitus.

Table 3: Clinical symptoms

Presenting symptoms	n	%
Respiratory symptoms		
Cough	71	72.45
Shortness of breath	65	66.33
Chest pain	31	31.63
Hemoptysis	4	4.08
Sore throat	1	1.02
Gastrointestinal symptoms		
Vomiting	6	6.12
Abdominal pain	5	5.10
Diarrhea	3	3.06
Nausea	3	3.06
Anorexia	3	3.06
Central nervous system		
Decreased level of consciousness	18	18.37
Headache	12	12.24
Seizures	5	5.10
Agitations	3	3.06
Dizziness	2	2.04
Other symptoms		
Body weakness	33	33.67
Rhinorrhea	9	9.18
Chills	2	2.04

The majority (72.45%) with severe COVID-19 presented cough, 66% presented shortness of breath and 31.6%, chest pain. Eighteen patients (18.37%) presented with decreased level of consciousness.

Table 4: Laboratory results and clinical assessment findings

Biochemical measurement s	n	%
qSOFA		
<2	57	58.16
2	33	33.67
3	8	8.16
SOFA score		
Median (Q1-Q2)	3 (3-6)	
UVA		
Median (Q1-Q2)	3.5 (2-6)	
Biochemical measurements		
Temperature in °C (n=81)		
Median (Q1-Q2)	37.6 (36.6-38.7)	
Bicarbonate in 20 mEq/L (n=7)		
Median (Q1-Q2)	18 (13.75-29.5)	
Hemoglobin in gr/dl (n=90)		
Median (Q1-Q2)	13.52 (11.8-15.15)	
Lymphocytes *10^9/L (n=90)		
Median (Q1-Q2)	0.91 (.62-1.60)	
Urea in mg/dl (n=82)		
Median (Q1-Q2)	6.5 (3.9-12.25)	
Creatinine in mmol/dl (n=87)		
Median (Q1-Q2)	77.8 (60.05-119.1)	
Sodium mEq/L (n=81)		
Median (Q1-Q3)	138 (132-142)	
ALAT in IU/L (N=83)		
Median (Q1-A3)	39 (19-71)	
Localized infiltrated % (n=23)		
Median (Q1-Q3)	25 (11-50)	
Bilateral infiltrates %		
Median (Q1-Q3)	67(50-86.25)	

The median SOFA score was 3 and the median UVA was 3.5, while the majority (58%) had qSOFA score of less than 2. The median urea measurement was 6.5 mg/dl and the median creatinine measurement was 77.8mmol/dl.

Table 5: Management of patients

	n	%
Oxygenotherapy with masks	84	85.7
Mechanical ventilation		
Oxygenotherapy using noninvasive Mechanical ventilation (NIV)	10	10.2
Oxygenotherapy using invasive Mechanical ventilation (IMV)	4	4.1
No pharmacology therapy	28	28.6
Pharmacological therapy		
Monoclonal antibodies	4	4.1
Antiviral therapy	61	62.2
Antiviral drugs combined to Monoclonal antibody	5	5.1

Only 14 patients underwent mechanical ventilation (14.3%) including 10.2% under NIV and 4.1% IMV. Remaining patients received Oxygenotherapy with facial masks 84(85.7%).

Table 6: Complications including death and length of stay

Complications	N	%
Respiratory failure	63	64.3
Non-ARDS	42	42.8
ARDS	21	21.4
AKI	19	19.39
Septic shock	9	9.18
Liver injury	4	4.08
Pulmonary embolism	5	5.10
Sepsis	5	5.10
Hyperglycemia	4	4.08
Final outcome		
Died	60	61.22
Survived	38	38.78
Hospital stay		
Median (Q1-Q3)	6 (3-10) days	

Amidst patients with severe or /and criticalCOVID-19, 64% developed respiratory failure, 21.4% of them were from ARDS, 19.39% developed AKI and 9% developed septic shock. The median hospital stay was 6 days and the mortality was high at 61%.

Table 7: Association of clinical and sociodemographic characteristics with mortality among patients with severe and critical COVID-19

Predictors	Final outcome		OR (95% CI)	P value
	Survived	Died		
Age in years				
≤35	5 (50.0%)	5 (50.0%)	Ref	
36-65	19 (44.19%)	24 (55.81%)	1.26 (0.32-5.01)	0.740
>65	14 (31.11%)	31 (68.89%)	2.21 (0.55-8.89)	0.263
Gender				
Male	16 (38.10%)	26 (61.90%)	1.05 (0.46-2.39)	0.905
Female	22 (39.29%)	34 (60.71%)	Ref	
Marital status				
Married	34 (37.78%)	56 (62.22%)	1.64 (0.38-7.02)	0.500
Single	4 (50.00%)	4 (50.00%)	Ref	
qsofa				
<2	34 (59.65%)	23 (40.35%)	Ref	
2	4 (12.12%)	29 (87.88%)	10.72 (3.3-34.5)	<0.001
3	0(0.00%)	8 (100%)	-	
Hypertension				
Yes	7 (29.17%)	17 (70.83%)	1.75 (0.64-4.73)	0.269
No	31 (41.89%)	43 (58.11%)	Ref	
Diabetes mellitus				
Yes	6 (35.29%)	11 (64.71%)	1.19 (0.40-3.56)	0.746
No	32 (39.51%)	49 (60.49%)	Ref	

Patients who scored 2 in qSOFA were 11 times prone to die set side by side with to those who scored less than 2 with a statistically significant difference (OR=10.72; 95% CI: 3.3-34.5; p<0.001). There was no statistically significant difference in mortality according to age, gender or having comorbidities.

Table 8. Association of clinical and biochemical measurements with mortality among patients with severe and critical COVID-19

Predictors	Final outcome		P value
	Survived	Died	
QSOFA score			
Median (Q1-Q3)	3 (2-3)	4 (3-7)	<0.001
UVA score			
Median (Q1-Q3)	2 (0-2)	6 (3-7.5)	<0.001
Body Temperature in ^{o}C			
Median (Q1-Q3)	37.8 (36.4-38.8)	37.5 (36.7-38.7)	0.912
Bicarbonate in 20 mEq/L (n=7)			
Median (Q1-Q2)	4.5 (3-6)	4 (2-5)	0.698
Hemoglobin in gr/dl (n=90)			
Median (Q1-Q2)	37.5 (25-50)	27.5 (12-51)	0.129
Lymphocytes *10^{9}/L (n=90)			
Median (Q1-Q2)	1.05 (0.72-1.57)	0.86 (0.58-1.62)	0.308
Urea in mg/dl (n=82)			
Median (Q1-Q2)	5 (3.5-6.7)	10.2 (5.5-15.4)	<0.001
Creatinine in mmol/dl (n=87)			
Median (Q1-Q2)	28 (15-48)	53 (41-68)	<0.001
Sodium mEq/L (n=81)			
Median (Q1-Q3)	137 (132-139.5)	138 (131-144)	0.251
ALAT in IU/L (N=83)			
Median (Q1-A3)	23 (15-44)	46 (26.5-106)	<0.001
Localized infiltrates % (n=23)			
Median (Q1-Q3)	0.25 (0.125-0.50)	0.25 (0.11-0.50)	1

The median SOFA score was high in non survivors juxtaposed to the median score of survivors ($p<0.001$) and the median UVA score was also high in non survivors set side by side with the one of survivors with a statistically significant difference ($p<0.001$). A statistically significant difference in median urea measurements of 10.2 mg/dl compared to 5mg/dl in survivors with $p<0.001$ was found and there was a statistically significant difference in median creatinine measurements where patients who died had the median creatinine of 53 mmol/dl compared to 28 mmol/dl in survivors ($p<0.001$). Patients who died also had high median ALAT measurement of 46 IU/L compared to 23 IU/L found in survivors ($p<0.001$). There was no statistically significant difference in median body temperature, bicarbonate, hemoglobin, lymphocytes, sodium and unilateral infiltrates.

Table 9. Multivariable logistic regression analysis of predictors of mortality among patients with severe and critical COVID-19

Predictor	AOR	95% CI	P value
qSOFA			
1	1.00	Ref	
2	3.13	0.5-17.37	0.192
SOFA Score	0.97	0.63-1.48	0.902
UVA	1.49	1.03-2.16	0.034
Hemoglobin	0.98	0.94-1.01	0.266
Urea	1.21	1.03-1.41	0.017
ALAT	1.01	0.99-1.03	0.144

The factors that showed association with mortality in severe and critical COVID-19 patients with $p<0.250$ were considered in the multivariable logistic regression analysis namely qSOFA, SOFA score, UVA, hemoglobin, urea, creatinine and ALAT. UVA score and urea measurements were predictors of mortality among severe and critical COVID-19 disease.

CHAP V DISCUSSION

The presented study recruited 98 patients and their median age was 63.5 (51-75) and 24.5% of patients had hypertension and 17.3% had diabetes mellitus. This was very similar to the study conducted in Iran which showed the median age was 62 (54-72)(24).This similarity is justified by the fact that people with advanced age are prone to present with severe or/and critical COVID-19 disease. One study done in Egypt showed the commonest comorbidities in patients who presented with severe or/and critical COVID-19 were hypertension at 47.8% and Diabetes mellitus at 46.3% (25), this discrepancy with our study may be justified by the small sample of our study as there was no room to expand the sample size. There was limitation to distinct patients with controlled and uncontrolled hypertension or/and diabetes.

The most common symptoms of severe and critical COVID19 were cough at rate of 72.5%, followed by shortness of breath at rate of 66%, while chest pain was at rate of 31.6% and general body weakness at rate 33.6%. The most common complications were respiratory failure at rate of 64.3% caused by ARDS in proportion of 21.4%, AKI at rate of 19.4% and septic shock at 9.18% .This is very closer to the multicenter control study conducted in Singapore which showed that the cough presented at rate of 77%, fever at rate of 78%, shortness of breath at rate 25% and ARDS at rate of 61%(26).It is very similar also to the systematic review which involved twelve studies conducted in China in 2020 and revealed that the most clinical symptoms were fever at rate 88.3%, cough at rate of 62.2%, dyspnea at rate of 31.5% while the most common complications were ARDS at rate of 22.2%, AKI at rate of 3.6% and shock at rate of 1.3%(27). This little difference in frequency of symptoms may due to the fact that patients are different and their immune response to infection may differ. The lower prevalence of complications compared to the present study may due to the advanced clinical management which can prevent further complications. Shortness of breath is among clinical manifestations linked to severe COVID-19 and patients presenting fever are at high risk to develop severe and critical COVID-19 disease(22). Similarly to the presented study, diarrhea was uncommon in other different studies(27). This study showed the median for localized infiltrates was 25 (11-50) and for bilateral infiltrates 67(50-86.25). Radiology findings change according to the age of patient, disease course , immunity status, comorbidities and first medical management(28), Chest X-ray findings are not well defined, and the early phases of the disease radiologic findings can be normal. The commonest findings include lobar or multi-lobar or bilateral lung

consolidation(13),COVID-19 patients manifested classic features on initial CT, made up of bilateral multi-lobar ground glass opacities along with peripheral/ posterior distribution (16). The presented study showed that more than three -quarter of the participants 84 (85.7%) received oxygenotherapy via masks. Only 14(14.2%) received respiratory support via mechanical ventilation. Most of the patients, 62.2% received antiviral drug while only 4.1% received monoclonal antibodies, and 5.1% received combination of antiviral drugs and monoclonal antibodies. The monoclonal antibodies have proven to decrease the rate of hospitalization and mortality in mild /moderate COVID-19 patients if they are administered within the 5 days of onset of symptom(8). This is comparable closer to the systematic review which involved twelve studies conducted in china in 2020 and showed 87.4% of the patient received antiviral therapy, 67.6% of the patient received oxygen by mask while 24.4% of patients received NIV and 8.4% received IMV (27). This higher prevalence of the management means used in China may be justified by the fact that our settings have limited resources compared to China. This study didn't evaluate the complications associated with the use of corticosteroids in diabetic and non-diabetics patients.

The majority of infected patients were aged > 50years [63.5(51-75)], however the mortality was not statistically associated to the advanced age. Different studies conducted in developed countries showed that the mortality is statistically associated to the advanced age and comorbidity(1)(21)(29) and age above 50 years was a factor leading to severity and survivors were younger than non-survivors in one study done in South of India(30).

More than half 60(61.2%) of patients admitted with severe or/and critical COVID-19 disease died and almost all death (59 over 60) were due to COVID-19. This mortality is very closer to the mortality of 57.9% reported in retrospective cohort study conducted in Tehran, Iran to assess features and outcome of critical patients with COVID-19 (26)(31). The revealed mortality from this presented study is similar to other studies done in developed countries(32)(25). The Median of LOS in HDU/ICU in days was 6(3-10) for this study. This is closer to one study done in Iran among 133 patients with severe COVID-19 pneumonia. However both studies did not found significant statistical association between hospitalization duration and mortality rate.

The higher level of ALAT and urea at admission due to insufficient oxygen supply to the kidneys and liver, and other complications like respiratory failure were found in high rate in non survivors and it is similarly to other systematic review and single studies(33)(34)(35)(36). The findings may be attributed to severe infection and the delay to consult the health facilities until different organ failure happened.

Even though the presented did not show statistical association between advanced age ,different comorbidities like hypertension / diabetes and COVID-19 patients related mortality like done in different single studies or systematic reviews(35)(37), the proportion of non survivors for the ones with hypertension was 70.8% and diabetes 60.4%. This is very closer to a single study done in Indonesia where rate of mortality was higher among COVID-19 patients with hypertension at 55.4%, diabetes at 37.3%(37).

In addition, the presented study showed that adjusted Odd ratio and 95% confidence interval of urea and UVA were associated with mortality. These results may be for the clinical importance in planning and preventing further deterioration of patients with COVID-19 by tackling each modifiable element of UVA score and encouraging people to consult health facilities early

CHAPTER VI: CONCLUSION AND RECOMMENDATIONS

The commonest features of severe and critical COVID19 were cough, shortness of breath, chest pain and general body weakness while the most common complications were respiratory failure from ARDS and other causes, AKI and septic shock.

There is a high mortality that could be predicted by higher Urea and UVA Score at admission in patients admitted for severe and critical COVID-19 disease at CHUB. Initial assessment can track patients at high risk of death and help to prevent it. Protocols and guidelines for special management for those who are at the risk of death are needed.

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Appendix 1: QUESTIONNAIRE

Questionnaire

A. Demographic characteristics

1 Age (in years):_____

2. Gender: Male ☐ Female ☐

3. Marital Status: Married ☐ Single ☐

4. Weight: __kg Height: _____cm Body mass index_____

5. Comorbidities

i. Hypertension: yes ☐ No ☐

ii. COPD: yes ☐ No ☐

iii. Diabetes: Yes ☐ No ☐

iii. Cancer: yes ☐ No ☐

iv. Chronic Liver disease: Cirrhosis, chronic liver disease, Hepatocellular carcinoma,..

v. Kidney disease: AKI, CKD

vi. Stroke

vii. Arrhythmia

viii. Pregnancy: ____weeks; postpartum: _____weeks

ix. Immunosuppression: HIV;

6. Covid 19 Vaccination status: Fist dose ☐ Second dose ☐ Third dose ☐ not ☐ vaccinated

7. Time of consulting health facilities after appearing of symptoms: (dd/mm/yyyy):……/…../…… at …:h……min (date of initial symptoms____/___/____;

8. Date of initiation of anti-COVID-19 treatment:___/___/_____

B. Severity of Disease

9. Table of QSOFA (Tick which item the patient has)

QSOFA score	0	1
Glasgow Coma Scale	15	<15
Respiratory rate	<22bpm	>22
Systolic blood pressure	>100mm Hg	<100mm Hg

10. Table SOFA (Tick which item the patient has where applicable)

SOFA Score	**1**	**2**	**3**	**4**
SpO2/FiO2 ratio (mmHg)	< 400	<315	<253*	<100*
Coagulation (platelet X $10^3/mm^3$)	<150	<100	<50	<20
Liver: Bilirubin; mg/dl **(mmol/L)**	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6-11.9 (102-204)	>12 (>204)
Cardiovascular: Hypotension	MAP<70mmHg	Dopamine ≤ 5 **ordobutamine	Dopa> 5 or Epi/Norepi≤ 0.1	Dopa>15 or Epi/Norepi>0.1
CNS: Glasgow Coma Scale (GCS)	13-14	10-12	6-9	≤ 5
Renal: Creatinine; mg/dl **(µmol/L)** **Urine output**	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) <500	>5 (>440) <200ml/24h

			ml/24h	

*Under respiratory support (Invasive, NIV or CPAP)

**Vasopressors or inotropes in µg/kg.min for at least 1 hour

11.Table UVA SOFA(Tick which item the patient has within 24hours of admission)

Points

Variables	0	1	2	3	4
Temperature(℃)	≥36		<36		
Heart rate (bpm)	<120	≥120			
Respiratory rate(pm)	<30	≥30			
Systolic blood pressure (mmHg)	≥90	<90			
Oxygen saturation (%)	≥92		<92		
GSC Score	15				<15
HIV infection	No/Unknown		Yes		

C. Signs and symptoms motivating the transfer

12. Fever: Yes ☐ No ☐

13. Respiratory symptoms:

14. Gastrointestinal symptoms:

Neurological symptoms:

16. Renal symptoms:

17. Cardiovascular symptoms:

18. Other:

D. Admitting laboratory investigations

19. Markers of Inflammation

i. D-Dimers

ii. CRP

iii. LDH

iv. Ferritin

v. Troponin I

20. Chest image finding Xray/ CT scan

i. Diffuse infiltrates in both lungs (%)

ii. More localized infiltrates (%)

iii. Existence of features of pulmonary embolism

E. Therapeutic intervention

21. Respiratory support

i. Invasive mechanical ventilation

ii. None invasive ventilation

iii. Oxygenotherapy by using non rebreather mask

iv. Oxygenotherapy simple mask

v. Oxygenotherapy by nasal canula

State all approaches used to support the patient in chronological order during her/his stay by using assigned number to each approach:..., …., …..,….,…..

22. Cardiovascular support, list all inotropes or vasopressors used

i. Shock: Cardiogenic ☐ Septic ☐

Ii. Inotropes:

iii. Vasopressors:

23. Renal support by hemodialysis Yes or No

24. Pharmacological therapies: Drugs

i. Favipiravir

ii. Ivermectin

iii. Azithromycin

iv. Tocilizumab

v. Bamlanivimab

F. Outcome

25. Number of days hospitalized after being diagnosed with COVID 19: LoS…..

26. Discharge disposition: Home: ☐ Ward: ☐ Transfer to Another tertiary Hospital: ☐
Discharged to district Hospital: ☐ Death: ☐

27. Covid 19 contributed to Death: Yes ☐ or No ☐

28. Complications (Tick all the patient presented)

i. Respiratory failure

ii. Acute Respiratory Distress Syndrome

iii. Disseminated intravascular coagulation

iv. Acute cardiac injury or myocardial stunning

v. Acute Kidney injury

vi. Septic shock

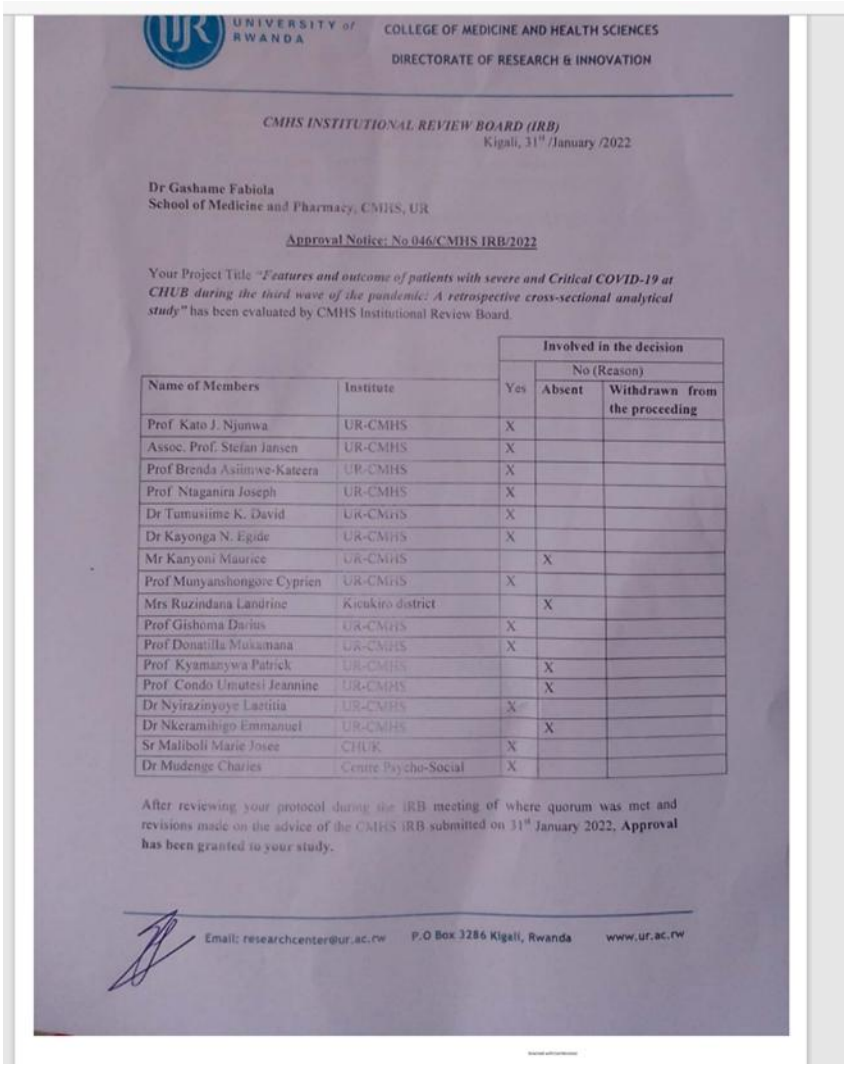
vii. Liver failure

vii. Pulmonary embolism

viii. Ischemic stroke

ix. Cardiogenic shock

Appendix 2: ETHICAL APPROVAL FROM IRB



UNIVERSITY of RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

DIRECTORATE OF RESEARCH & INNOVATION

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 31st /January /2022

Dr Gashame Fabiola
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 046/CMHS IRB/2022

Your Project Title *"Features and outcome of patients with severe and Critical COVID-19 at CHUB during the third wave of the pandemic: A retrospective cross-sectional analytical study"* has been evaluated by CMHS Institutional Review Board.

		Involved in the decision		
			No (Reason)	
Name of Members	**Institute**	Yes	**Absent**	**Withdrawn from the proceeding**
Prof Kato J. Njunwa	UR-CMHS	X		
Assoc. Prof. Stefan Jansen	UR-CMHS	X		
Prof Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS		X	
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Ruzindana Landrine	Kicukiro district		X	
Prof Gishoma Darius	UR-CMHS	X		
Prof Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 31st January 2022, **Approval has been granted to your study.**

Email: researchcenter@ur.ac.rw P.O Box 3286 Kigali, Rwanda www.ur.ac.rw

Please note that approval of the protocol and consent form is valid for **12 months**.

You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval
5. Failure to submit a continuing review application will result in termination of the study
6. Notify the IRB committee once the study is finished

Sincerely,

Date of Approval: The 31st January 2022

Expiration date: The 31st January 2023

Assoc. Prof. Stefan Jansen
Ag. Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Cc:
- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR

Appendix 3: ETHICAL APPROVAL FROM CHUB

CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

CLINICAL EDUCATION AND RESEARCH DIVISION
RESEARCH DIRECTORATE
RESEARCH -ETHICS COMMITTEE

Huye, March 21, 2022

Approval Notice: No: REC/UTHB/088/2022

Dr. Dona Fabiola GASHAME
Master of Science in anesthesiology
University of Rwanda

Reference is made to your letter requesting for data collection approval of your study Entitled ***"Features and outcome of patients with severe and Critical COVID-19 at CHUB during the third wave of the pandemic: A retrospective cross-sectional analytical study." once given ethical clearance from CHUB."***

Having reviewed your application and been satisfied with your protocol, your study is hereby granted ethical clearance and should be conducted within University Teaching Hospital of Butare

Please note that approval of the protocol and consent form is valid for one year starting on the issue date and shall be renewed on request.

You are responsible to fulfilling the following requirements:

- Changes, amendments and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes
- Only approved consent forms are to be used in the enrollment of participants
- All consent forms signed by subjects should be retained on file. The committee may conduct audits of all study records. Consent documentation may be part of such audits
- A continuing review application must be submitted to the committee in a timely fashion and before expiry of this approval
- Failure to submit continuing review application will result in termination of the study
- Notify the committee once the study is finished and wherever necessary
- Identification of participants must be kept confidential for the duration of the study.

Sincerely

Dr. HABIMANA Emmanuel
Chairperson of Research -Ethics Committee/CHUB

Digitally signed by HABIMANA Emmanuel
Date: 2022.03.23 20:13:08 +02'00'

Cc:

- ✓ Director General
- ✓ Head of Clinical Education and Research Division
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