CHEST RADIOGRAPHIC SCORES AT ADMISSION CORRELATED TO THE MORTALITY OF COVID-19 PATIENTS AT THE KENYATTA NATIONAL HOSPITAL

DR. ESTHER.C.M. GUMBE
H58/11901/2018
DEPARTMENT OF DIAGNOSTIC RADIOLOGY

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT FOR THE AWARD OF MASTER OF MEDICINE IN DIAGNOSTIC IMAGING AND RADIOLOGY MEDICINE, FACULTY OF HEALTH SCIENCES, UNIVERSITY OF NAIROBI

STUDENT' S DECLARATION

I**, Dr. Esther C. M. Gumbe**, do declare that the work contained herein is my original idea and has not been presented at any other university or institution of higher learning to the best of my knowledge**.**

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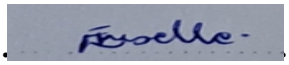
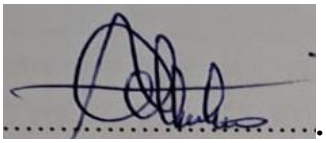
Signature: …  **…… Date: 9th November 2022**

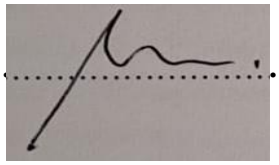
SUPERVISORS' APPROVAL

This dissertation has been submitted with our approval as the university supervisors.

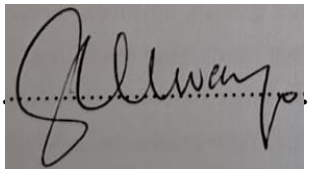
Dr. Alfred Odhiambo, MBChB, M.Med. Diagnostic Imaging (UoN)
Lecturer, Department of Diagnostic Imaging and Radiation Medicine, Faculty of Health Sciences, University of Nairobi.

Signature:  **.** **Date: 10/11/2022**

Dr. Beatrice Mugi, MBChB, MMed. Diagnostic Imaging (UoN)
Consultant Radiologist, Department of Diagnostic Radiology, Kenyatta National Hospital

Signature……  **……** **Date :** ***9th November, 2022***

Dr. Gladys Mwango, MBChB, M.Med. Diagnostic Imaging (UoN)
Senior Lecturer, Department, Diagnostic Imaging and Radiation Medicine, Faculty of Health Sciences, University of Nairobi.

Signature: …  **……** **Date: 11th Nov, 2022**

DECLARATION OF ORIGINALITY

Name:	**DR. ESTHER.C.M. GUMBE**
Reg Number:	**H58/11901/2018**
College :	Health Sciences
School:	Medicine
Department:	Diagnostic Imaging and Radiology Medicine
Course Name:	Master of medicine in Diagnostic Imaging and Radiology Medicine
Title:	**CHEST RADIOGRAPHIC SCORES AT ADMISSION CORRELATED TO THE MORTALITY OF COVID-19 PATIENTS AT THE KENYATTA NATIONAL HOSPITAL**

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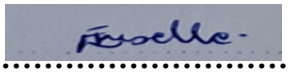
Signature: ……  **Date: 9th November 2022**

DEDICATION

This dissertation is dedicated to my parents. My mother **Dorry Mbelle** for her unwavering support. My father **Lawrence Gumbe** for paving the way.

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My utmost gratitude goes to my supervisors; **Dr. Mwango, Dr. Odhiambo** and **Dr. Mugi** for their support and their invaluable input. My research assistants, for availing the requisite radiographs and medical records

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LIST OF ABBREVIATIONS AND ACRONYMS

ACE2	Angiotensin converting enzyme 2
AP	Antero-posterior
ARDS	Acute respiratory distress syndrome
BSTI	British society of thoracic imaging
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CT	Computed tomography
GGO	Ground glass opacity
KNH	Kenyatta National Hospital
LDH	Lactate dehydrogenase
NLR	Neutrophil to lymphocyte ratio
PA	Postero-anterior
RALE	Radiographic assessment of lung edema
RT-PCR	Reverse transcriptase polymerase chain reaction
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
SpO_2	Oxygen Saturation
UON	University of Nairobi
WHO	World health Organization

ABSTRACT

Background: The chest radiograph is a common diagnostic modality used in the assessment and management of pulmonary infections. Chest radiography is therefore, often the first imaging investigation obtained in the diagnostic workup of admitted COVID-19 patients. This allows an assessment of the degree of pulmonary disease and also an early evaluation of the patient's prognosis. This study determined the effectiveness of chest radiography in the early prognostication of COVID-19 disease by correlating the chest radiographic scores at admission with the mortality of RT-PCR confirmed COVID-19 patients.

Objective: Correlation of the chest radiographic scores at admission to the in-hospital mortality of COVID-19 patients.

Materials and Methods: A retrospective cross-sectional study was carried out in the Radiology Department and the Health Information Department of the Kenyatta National Hospital from 1st May 2020 to 31st April 2021. A total of 246 RT-PCR confirmed COVID-19 patients aged above 18 years were recruited into the study and their initial chest radiographs at admission were evaluated. A modified RALE chest radiograph severity score, of 0–8 was used to quantify the extent of pulmonary involvement. Correlation of the chest radiographic scores and the in-hospital mortality was done using chi-square tests.

Results: A total of 246 patients with COVID -19 PCR positive were included in this study. The male to female ratio was 1:5:1. The mean age was 47.6 years (SD=14.3). The admission chest radiographs evaluated in this study were 246 of which 43.1% (106/246) were normal chest radiographs and the remaining 56.9% (140/246) radiographs had positive findings. Among the chest radiographs with positive findings, 45.7% (64/140) chest radiographs demonstrated a Modified RALE score of (1-4) while 54.3% (76/140) chest radiographs had a score of (5-8). The overall mortality rate was 12.6%. The mean age of the in-hospital mortalities was 55.3±17.4 whereas the mean age of the discharged patients was 46.5±13.5, (p-value of 0.011). Patients with RALE scores of 7 and 8 were 4.3 times (95% CI, 1.3 – 13.8, p=0.015) and 3.5 times (95% CI, 1.3 – 9.7, p=0.014) more likely to have in-hospital mortality when compared with the reference group of patients with RALE scores of between 0 to 4.

Conclusion: This study shows that the highest RALE scores of 7 and 8 at admission posed a statistically significant increased risk of mortality at 4.3 times and 3.5 times respectively in comparison to the scores of 0-4. The Modified RALE chest radiographic scoring can be an invaluable tool in high- volume, resource constrained settings in providing rapid and objective prognostic information in the management of COVID-19 patients.

1.0 CHAPTER ONE: INTRODUCTION AND BACKGROUND

The coronavirus disease 2019 (COVID-19) is a highly transmissible and lethal viral illness caused by the beta coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Lung infection may lead to severe pneumonia which can cause an aggressive acute respiratory distress syndrome (ARDS)(1).Outbreaks of the coronavirus disease 2019 were first reported in the Wuhan area of China at the end of 2019.The cases have rapidly spread to many parts of the world. The World Health organization recognized the upsurge of the global COVID-19 cases as an international public health threat. COVID-19 would then be declared a global pandemic by the World Health Organization in March 2020 (2).

The first confirmed case of COVID-19 in Kenya was reported on the 12th March 2020 (3).As of 5th July 2021, there were 186,053 total confirmed COVID cases in Kenya(4). The cumulative COVID-19 mortalities in Kenya, as reported on 5th July 2021 were 3690 (4). The cumulative fatalities due to COVID- 19 in Africa were 140,040 as reported on June 24, 2021(5).South Africa reported the highest number of COVID -19 fatalities with 59,406 deaths(5). As of June 24, 2021, Africa had recorded more than 5.36 million cases of COVID-19(5). Globally, as of 5th July 2021, there were 183,560,151 confirmed cases of COVID-19 reported (6). The global death toll from COVID was reported as 3,978,581 deaths (6). In a study by Piroth *et al*, it was demonstrated that the inpatient mortality rates for COVID-19 patients exceeded those of the seasonal influenza by a factor of three (7).

The molecular test, reverse-transcription-polymerase-chain-reaction assay (RT-PCR) is accepted as the definitive diagnostic standard in the detection of COVID-19 illness (8). However, the long turnaround times and the large number of false negative results restrict the utility of the reverse-transcription-polymerase-chain-reaction (RT-PCR) test (1). Computed tomography (CT) has proven to be more sensitive than chest radiography in detecting imaging features of COVID-19,but it is more costly, less available, provides a higher risk of cross-infection and it is also less specific than the chest radiograph(9).Conversely, considering its portability, wide availability, speed, and low costs, chest radiography is often the first imaging investigation for COVID-19 patients.

Several chest radiographic severity scoring systems have been developed with the aim of providing prognostic indicators in the management of COVID-19 patients (8,10). Kaleemi *et al*, utilized the modified RALE scoring system to demonstrate a positive correlation between the highest chest radiographic scores and in-hospital mortality among COVID-19 patients (11). Similarly, in the same study, the greater chest radiographic severity scores were positively

associated with higher rates of intensive care admissions (11). Borghesi *et al* showed that a combination of a high Brixia score with an additional poor prognostic indicator such as advanced age or immunosuppression, demonstrated the greater risk of mortality among COVID-19 patients (12). Furthermore, in another study, it was demonstrated that the highest chest radiographic scores combined with the clinical frailty status and presence of fever were significant predictors of in-hospital mortality among older hospitalized patients with COVID-19(13).In a study by Reeves *et al*, the highest chest radiographic scores at admission were positively correlated to in-hospital mortality(14). Additionally, this study demonstrated that this association was independent of a range of demographic factors as well as laboratory and clinical factors from the time of presentation(14).

Kenya is a resource limited setting. Early prognostication of COVID-19 would help in appropriate resource allocation. This is especially important when a surge in cases puts a strain on hospitals, overcrowding wards and Emergency departments, and reducing bed availability. Therefore, making it even more important to be able to quickly and reliably distinguish those who need aggressive hospital care from those who can be treated conservatively.

By correlating the chest radiographic scores at admission with the in-hospital mortality of COVID-19 patients, this study aims to determine whether the chest radiographic score at admission can be a prognosticator of mortality in the management of COVID-19.

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 The Trends of COVID-19 in Kenya

The first confirmed case of COVID-19 in Kenya was reported on the 12th March 2020 (3).The COVID- 19 cases would increase peaking to a positivity rate of 7.9% in August 2020 (15). The positivity rate of COVID-19 would then decrease to 4% in September (16).Thus marking the end of the first wave.

The COVID-19 positivity rate is defined as the percentage of positive RT-PCR tests (17).

The positivity rate of COVID-19 in Kenya would increase from a paltry 4% in September 2020 to 16% in October 2020, therefore marking the commencement of the second wave of COVID-19 infections in Kenya (16). By January 2021, the COVID-19 positivity rate was much lower at 2.6 % (18).

However, in March 2021, the Ministry of Health confirmed that Kenya was in its third wave of the Pandemic (19). In March 2021, Kenya experienced its peak positivity rate, since the onset of the pandemic (18).As of March 22nd 2021, the positivity rate was at 22%.

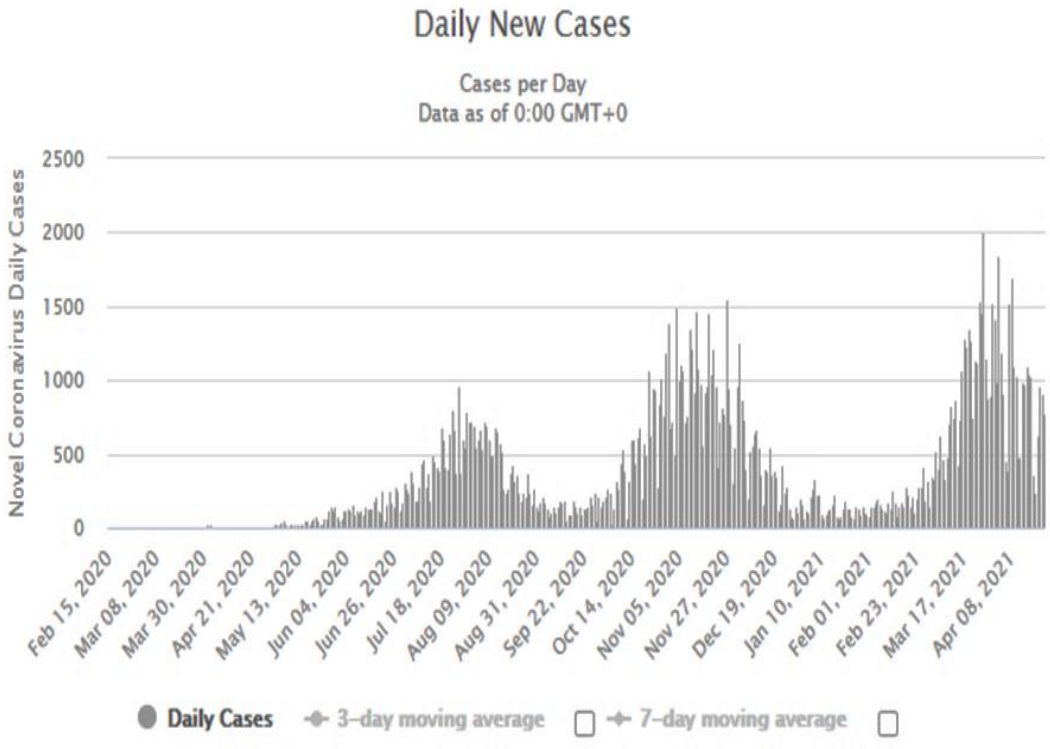


Figure 1:Graphic representation of daily COVID-19 cases in Kenya (5)

Above is a graphic representation of the daily cases of COVID-19 in Kenya. The graph, demonstrates the first wave beginning with the first confirmed case in March 12th 2020, peaking in August 2020 and a subsequent decrease of infections in September 2020.Also demonstrated is the second wave that peaked between October 2020 and November 2020, with decreased number of infections seen in January 2021. By Mid-March 2021, there was an upsurge of COVID-19 infections, marking the commencement of the third wave of COVID-19 infections in Kenya.

2.2 Diagnosing COVID-19

SARS-CoV-2 is primarily transmitted by respiratory aerosols acquired by close proximity interactions (20). It takes approximately 3–7 days from the time of the initial infection to the appearance of the first symptoms of COVID-19 (20). COVID-19 patients present primarily with fever, cough, chest pain, muscle pain, dyspnea and gastrointestinal symptoms (21). These patients also have markedly reduced lymphocyte counts, elevated hepatic enzymes and increased levels of inflammatory biomarkers(22).The molecular test, reverse-transcription-polymerase-chain-reaction assay (RT-PCR) is accepted as the definitive diagnostic standard in the detection of COVID-19 illness(8). However, the long turnaround times and the large number of false negative results restrict the utility of the reverse-transcription-polymerase-chain-reaction (RT-PCR) test (1). Several factors contribute to the high false negative results seen in reverse-transcription-polymerase-chain-reaction (RT-PCR) test. The sample type determines the accuracy of the RT-PCR test, with the bronchoalveolar lavage fluid demonstrating the highest sensitivity at 93%, while blood samples show the least sensitivity at 1% (23,24).Additionally, the levels of viral loads affect the sensitivity of the RT-PCR test (23,24).Patients recovering from COVID-19 with subsequently lower viral load levels, demonstrate a decreased sensitivity to the RT-PCR test (23,24). The high false negative results of the RT-PCR are also largely attributable to inappropriate methods of sample collection, transportation and handling (23,24).

The Fleischner Society is an international multidisciplinary medical society for thoracic radiology(25). It primarily provides guidelines that focus on the diagnosis and treatment of diseases of the chest. It draws its membership from radiologists, pathologists and chest physicians (25). In keeping with infection prevention protocols, the Fleischner society prohibits the use of the chest CT scan as a screening tool for COVID-19 patients(22). Furthermore, the Fleischner society recommends the use of chest radiography as a primary investigation tool, among COVID- 19 patients presenting with respiratory embarrassment, in resource-

constrained countries (26). The diagnostic sensitivity of the RT-PCR test in detecting COVID-19 is much lower than that of the chest CT scan (21).

Portable radiography enables the evaluation of critically ill patients who are not able to access the radiology units. As opposed to the chest CT, the Chest X-ray equipment is easy to sanitize. Chest radiographs are also relatively inexpensive (27). The Chest x-ray had a sensitivity of about 69% in the initial diagnosis of COVID-19 (21). In comparison to the chest CT, chest radiography appears to have a lower sensitivity but shows a higher specificity (27).Chest radiography provides lower radiation doses as opposed to Chest CT, and can be easily used in the sequential monitoring of disease progression (27)

2.3 Pathophysiology

In the respiratory tract and the lungs, the SARS-COV-2 virus interacts with multiple cells. These cells include the epithelial cells of the airways and the alveoli, vascular endothelial cells and macrophages. All these cells bear a common denominator-they all express the angiotensin-converting enzyme 2 (ACE2) receptor. It is postulated that the SARS-COV-2 interacts with the ACE2 receptor to gain entry into the aforementioned host cells. This is achieved by the interaction of the host ACE2 receptor and the SARS -COV-2 surface spike(S) protein as illustrated in figure 2 (28) .

Once the of SARS-COV-2 infection is established, the host mounts an immune response that culminates in the production of cytokines and also the activation of the immune responses of the T and B cells. The expected consequence of the robust immune activation is the resolution of the infection. Most patients therefore swiftly recover. In a small subset of patients, deranged immune responses cause a cytokine storm that mediates pulmonary destruction with the eventuality of pulmonary oedema. Pulmonary oedema compromises alveoli gaseous exchange leaving the patients hypoxic and vulnerable to secondary infections. The cytokine storm has far reaching consequences to the host, other than those seen in the respiratory tract. Cytokines such as tumor necrosis factor can facilitate multi-organ injury and failure. The cytokine storm can precipitate a septic shock causing much morbidity and mortality to the affected patients as illustrated in figure 3 (28).

Patients at the greatest risk of experiencing the deranged immune responses are those who are advanced in age, and those living with underlying comorbidities (28).

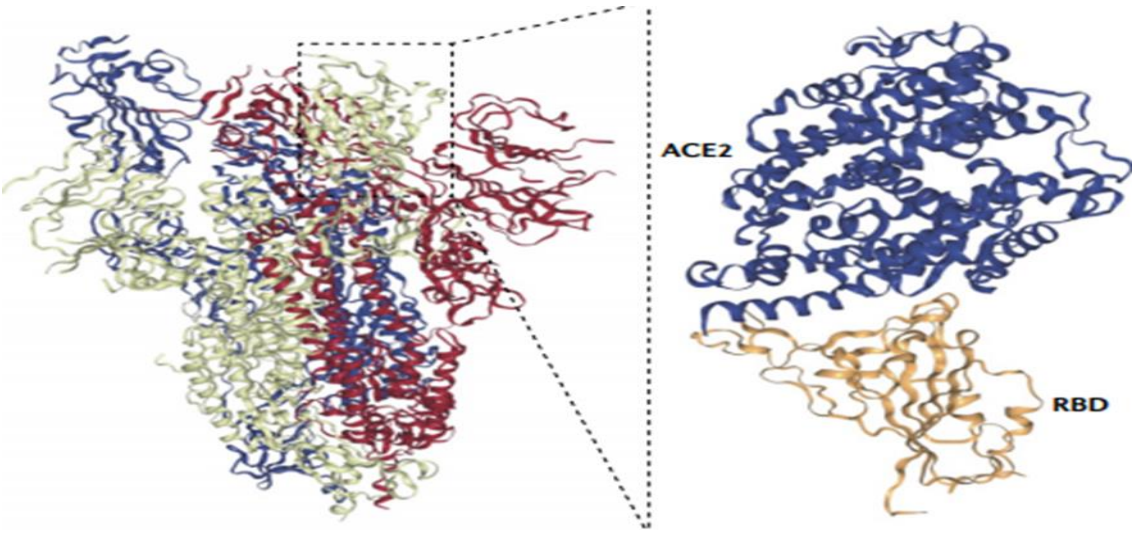


Figure 2:The host receptor ACE2 interacting with the spike protein of the SARS-COV2 (23)

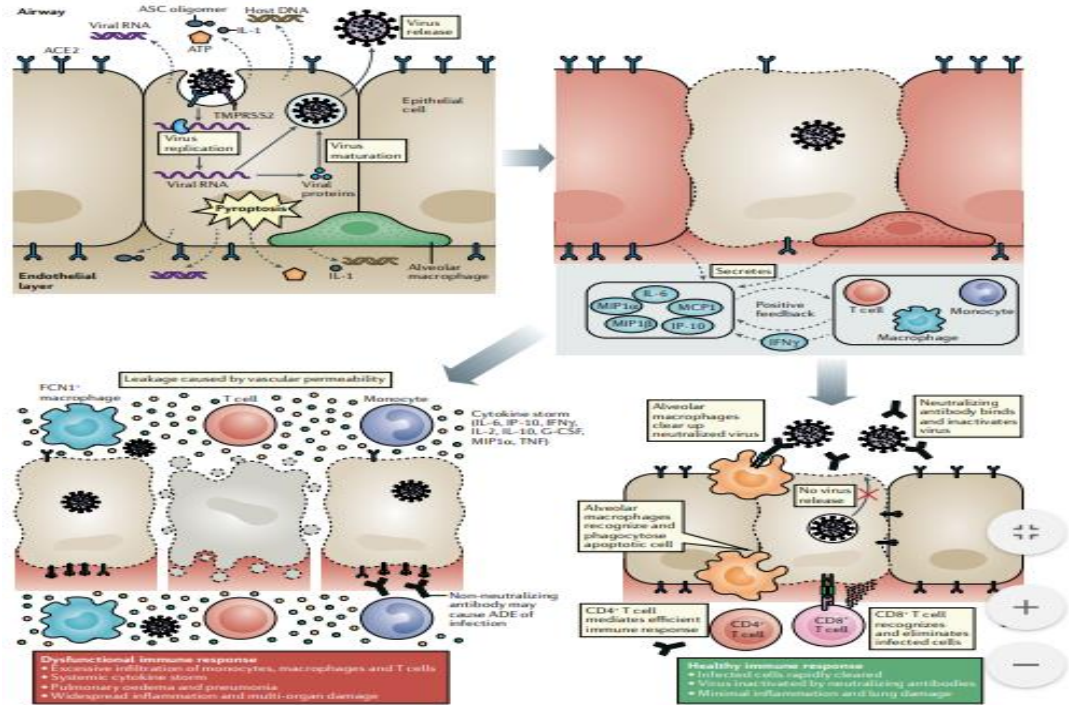


Figure 3:Illustration of the pathophysiology of COVID-19 (23)

2.4 Epidemiology of COVID-19

The Incubation period of COVID-19 illness, defined as the time from the infection with the virus to the onset of symptoms was 2 to 14 days (29). 81% of patients report a mild illness, while 5% progress to severe illness. In the critically ill patients, half of them will die of COVID-19 (30). The primary routes of transmission of COVID-19 are droplet and contact transmission. There is a plausible but unproven possibility of fecal transmission (31). There are no documented cases of antenatal mother to child transmission of COVID-19 (31).

The "basic reproduction number" termed R_0, is defined as the anticipated number of infectious cases engendered by one infected person, in a population of people equally vulnerable to a particular pathogen (29). Prior coronaviruses epidemics revealed a R_0 of 2, whereas in the current COVID-19 pandemic, the index is higher at 2.2. SARS-COV-2 is therefore, more infectious (29).

2.5 HIV and COVID-19 co-infection

Among persons living with HIV, the male sex was more predisposed to COVID-19 infections, replicating a similar pattern seen in the general population(32). However, the persons with HIV co-infected with COVID-19 were approximately 10 years younger than those infected with COVID-19 in the general population (32).

HIV infection is not considered a comorbidity that increases the risk of severe COVID-19 disease(32).Patients living with HIV had lower rates of death and hospital admissions when co-infected with COVID-19 when compared to HIV negative COVID-19 patients of a similar mean age(32).

HIV-positive patients co-infected with COVID-19 infection were not at a greater risk of severe disease or death than HIV-negative patients (32).

The radiographic findings seen in patients co-infected with HIV and COVID-19 are similar to those seen in the general population(33).No local studies have been done to demonstrate the radiographic effects of HIV and COVID-19 co-infection.

2.6 The Escalating Phases of COVID-19 Infection

There are three stages of escalating intensity seen in COVID-19 infection. Each stage has distinct clinical manifestations. The management of COVID-19 patients is customized to their respective clinical stages (30).

2.6.1 Phase 1— Establishment of Infection

Earlier on in the course of the COVID-19, patients present with non-productive cough, lethargy and mild fevers. The treatment at this non-specific early phase is geared towards supportive management. Most patients have very good outcomes.

2.6.2 Phase 2- Viral Pneumonia

High rates of viral replication are seen within the lungs. Subsequently a viral pneumonia develops. This phase categorizes patients in to two subgroups- those with no need for supplemental oxygen and those in dire need of mechanical ventilation. On chest imaging

bilateral multifocal areas of consolidation are seen, also seen are bilateral multifocal areas of peripheral ground glass opacities. The laboratory profile of patients in this phase shows decreased lymphocyte counts, elevated hepatic enzymes and slightly elevated inflammatory markers.

2.6.3 Phase 3—Extrapulmonary Manifestations

In this final phase, aggressive inflammatory responses are seen in multiple organs and systems. It is postulated that almost 5% of COVID patients progress to this phase. There is an upsurge in the inflammatory markers seen in elevated levels of interleukins, C-reactive protein, lactate dehydrogenase, ferritin and D-dimers. The severity of the illness is typified by respiratory embarrassment and septic shock. Treatment is catered to the regulation of the immune responses by the use of corticosteroids and immune globulin. The prognostic indicators and recovery are dismal.

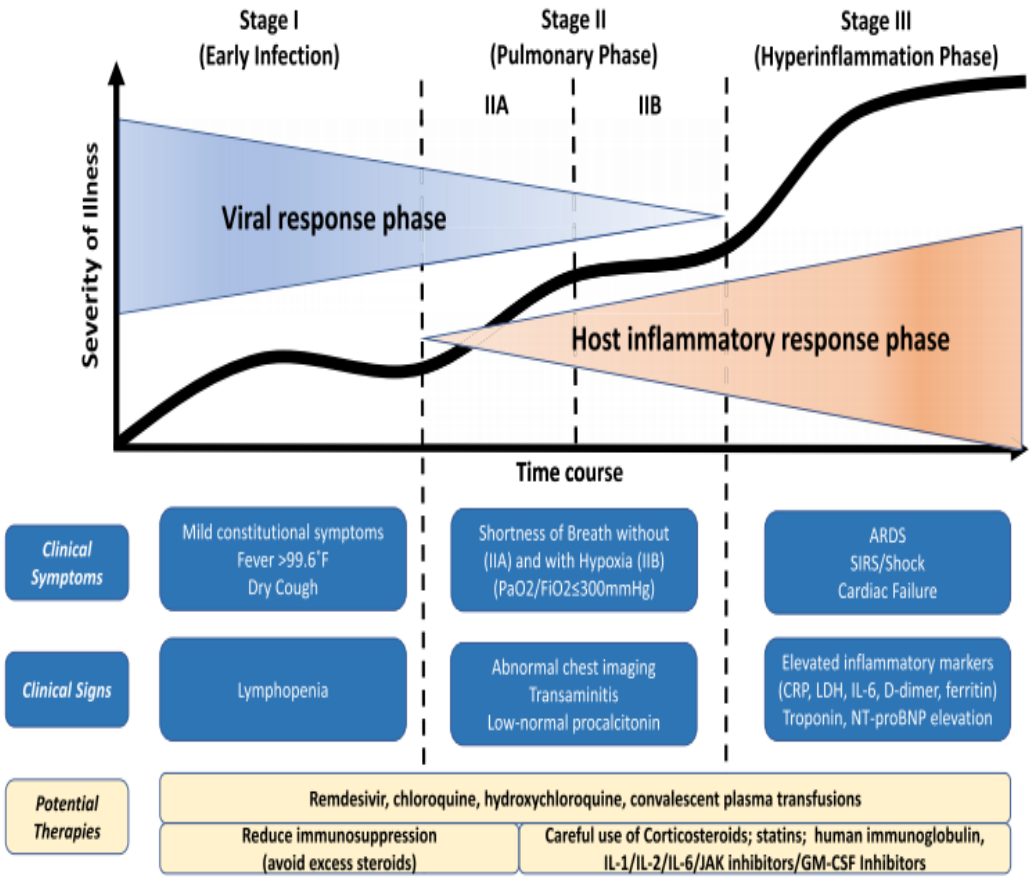


Figure 4:The escalating categories of COVID-19 with their respective therapies

2.7 COVID-19 Mortality

As of 5th July 2021 there were 3690 COVID-19 mortalities in Kenya (4).The global death from COVID-19 stood at 3,978,581 deaths as of 5th July 2021 (6). Several risk factors have been identified that increase the likelihood of death among COVID-19 patients. In a multicenter study, involving the Kenyatta National Hospital and other centers, Ombajo *et al* showed that the risk of mortality increased with age (34). The COVID-19 patients at an increased risk of death were those older than 60 years of age (34). Men were also at a greater risk of mortality than women. Those with an underlying comorbidity were also less likely to survive (34).Symptomatic COVID-19 patients were at a greater risk of mortality than asymptomatic patients (34). Ombajo *et al* also demonstrated that laboratory biomarkers were useful as predictors of mortality in COVID-19 patients.

Reduced lymphocyte counts, low haemoglobin levels and elevated hepatic enzymes were all demonstrated to increase the risk of mortality of COVID-19 patients (34). Similarly Grasselli *et al* demonstrated that underlying comorbidities were significant predictors of mortalities in COVID-19 patients (35).In the same study, male COVID-19 patients and patients above the age of 65 were at increased risk of mortality (35). COVID-19 patients with low oxygen saturation levels demonstrated an increased risk of mortality(36). The association of hypoxemia with increased likelihood of mortality was also seen in COVID-19 patients with silent hypoxia(36). The patients with silent hypoxia do not present with shortness of breath (36). Elevated glucose levels and low platelet levels were also associated with an increased risk of mortality(36).Elevated blood urea nitrogen and elevated levels of creatinine seen in impaired kidney function, increase the risk of mortality in COVID-19 patients (36).

Several studies have demonstrated a positive correlation between the highest chest radiographic scores at admission with an increased risk of mortality of COVID-19 patients (11–14)(37).

2.8 Professional Body Recommendations

Following the advice of the World health Organization (WHO), chest imaging is done where there is a lack of the RT-PCR tests. This could be in circumstances whereby the testing kits are insufficient, or in light of the long turnaround times of the RT-PCR test. In circumstances whereby the RT-PCR results are suspected to be falsely negative, Chest imaging is similarly advised by the World Health Organization (WHO) (27).

The Fleischner Society, in a multinational consensus statement, also advocates for chest imaging as a rapid modality of clinical triage of patients in resource-limited settings, when the RT-PCR COVID-19 testing is unavailable(26).Chest radiography is a preferred imaging modality by the World Health Organization(WHO) due to its large availability in resource-constrained settings, and also because, it provides lower radiation doses in comparison to Chest CT (27).

Chest radiographs are unnecessary in patients in the earlier phase of COVID-19 illness, with mild and non-specific features and no underlying risks for severe disease(26)**.** However, in the event of disease progression, the Fleischner Society recommends chest imaging. (26).

2.9 Variations of Chest Radiography Features in COVID-19

The radiographic alterations demonstrated in COVID-19 are defined with regards to the glossary of terms stipulated by the Fleischner's Society (38).

In a study by Wong *et al,* of confirmed COVID-19 positive patients (RT-PCR assay positive), the following chest radiographic findings were seen: Consolidation was the commonest finding seen in 30 of the 64 patients (47%), followed by ground-glass opacities seen in 21 of the 64 patients (33%). The consolidation and ground glass opacities seen were peripherally situated in both lung fields. It was also demonstrated that there was a predilection for both lower lung zones(10).

In the same study, pleural effusion was noted to be uncommon at chest radiography. The radiographic alterations were most marked at days 10-12, from the initial presentation of the symptomatology(10). The sensitivity of the chest radiograph was 69% as opposed to the 91% sensitivity of the RT-PCR test(10).In a retrospective study at a tertiary teaching hospital in the North part of Jordan by Rousan *et a*l, the commonest chest radiographic finding seen was ground glass opacity (GGO)(21).However this study, showed a similar distribution pattern as depicted by Wong *et al* . When only one lung was afflicted by COVID-19, it was the right lung that was affected, with a similar predilection for the lower zones(21).

In a study by Cozzi *et al,* Chest radiographic findings showed a bilateral distribution pattern with a preponderance to afflict the lower lung zones. The radiographic alterations demonstrated were reticular–nodular opacities and consolidation. As previously demonstrated in unilateral disease, there was a predilection for the right lung[(1)].Multiple other studies have shown a similar pattern of distribution of chest radiographic findings, with infrequent incidences of pleural effusion (39) (20).

In a study to assess the time-dependent radiographic alterations seen in COVID-19 illness, the following progression was demonstrated: Earlier on in the illness, the main features were reticulations which would then progress into ground glass opacities in the later phases of the illness. Rarely was consolidation seen (40). This pattern of radiographic disease progression was replicated in another study that demonstrated the most marked radiographic alterations at days 5-10 from the initial presentation of symptoms(21).

2.10 COVID-19 Scoring Systems

Several chest radiographic severity scoring systems have been developed with the aim of providing prognostic indicators in the management of COVID-19 patients(8,10). In a study by Toussie et al, it was demonstrated that there was a positive correlation between the severity of lung scores with the requirement for admission and mechanical ventilation (41). Hui et al demonstrated that the highest radiographic scores were positively associated with markedly elevated biomarkers of inflammation such as C-reactive protein and lactate dehydrogenase (42).Conversely, the highest radiographic scores were associated with markedly reduced lymphocyte counts patients(42). The highest lung severity scores increased the likelihood of inpatient care and intubation for mechanical ventilation(42). Additionally, Hui et al demonstrated a negative correlation between the highest chest radiographic scores and the oxygen saturation levels seen among COVID-19 patients (42).

2.10.1 The Modified Radiographic Assessment of Lung Oedema

This was a radiographic severity scoring system developed by Wong et al to stratify RT-PCR confirmed COVID-19 patients (10). Both lungs were evaluated individually. The extent of opacification or haziness was then quantitively graded. A score of 0 to 4 points was given (0 – no involvement; 1 – less than 25%; 2 – 25% to 50%; 3 – 50% to 75%; 4 more than 75% involvement). The severity score was the sum of what was given to the left lung and the right lung (10).The highest severity score given to a particular chest radiograph is 8.

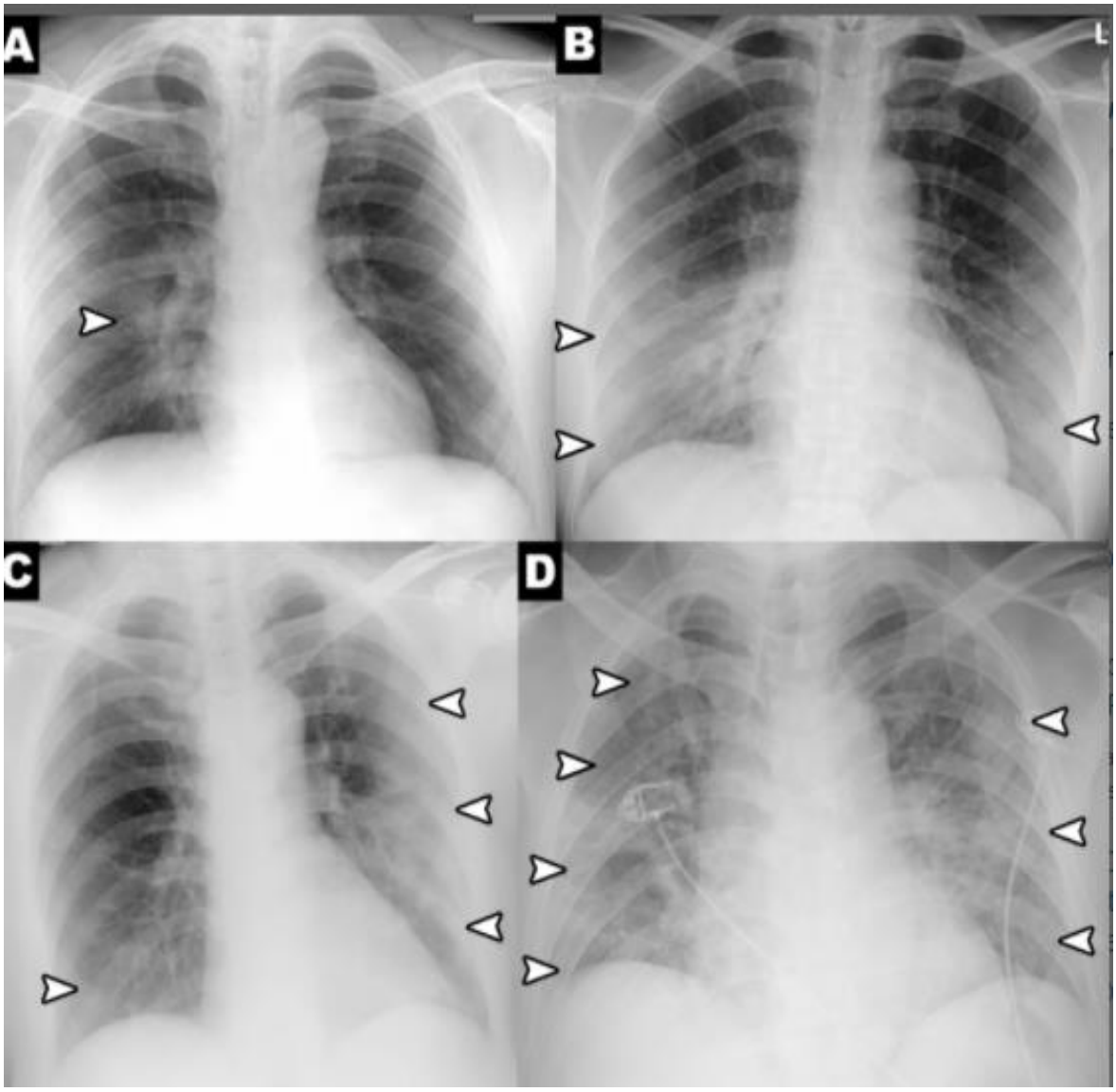


Figure 5: Examples of the modified radiographic assessment of lung oedema (10)

The arrowhead demonstrates lung opacification. In A less than 25% of the right lung was involved therefore the score is 1. In *B*, less than 50% of right lung was opacified, in the left it was less than 25% the total score was 3. In *C*, less than 25% of right lung was involved and more than 50% of left lung, total score was 4. In *D*, more than 75% of the right lung with more than 50% of the left lung total score was 7.

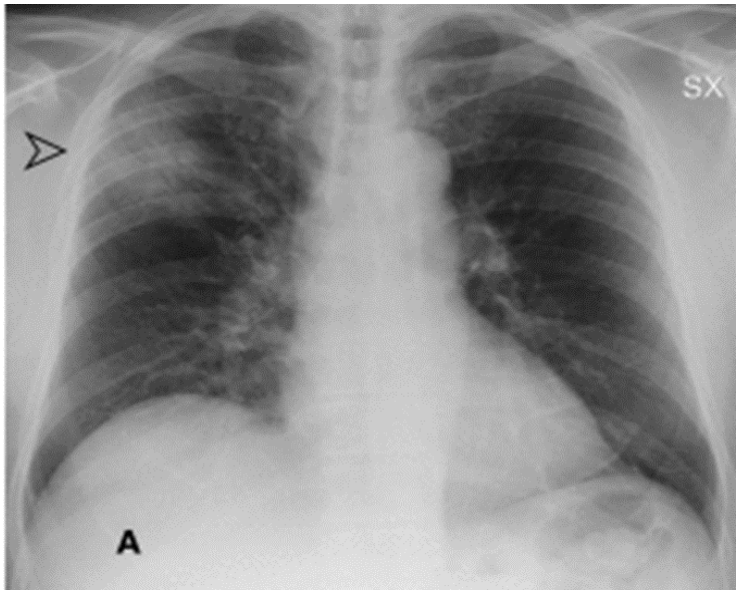


Figure 6:Area of ground glass opacity seen in the right upper zone is less than 25%, the score is 1(10)

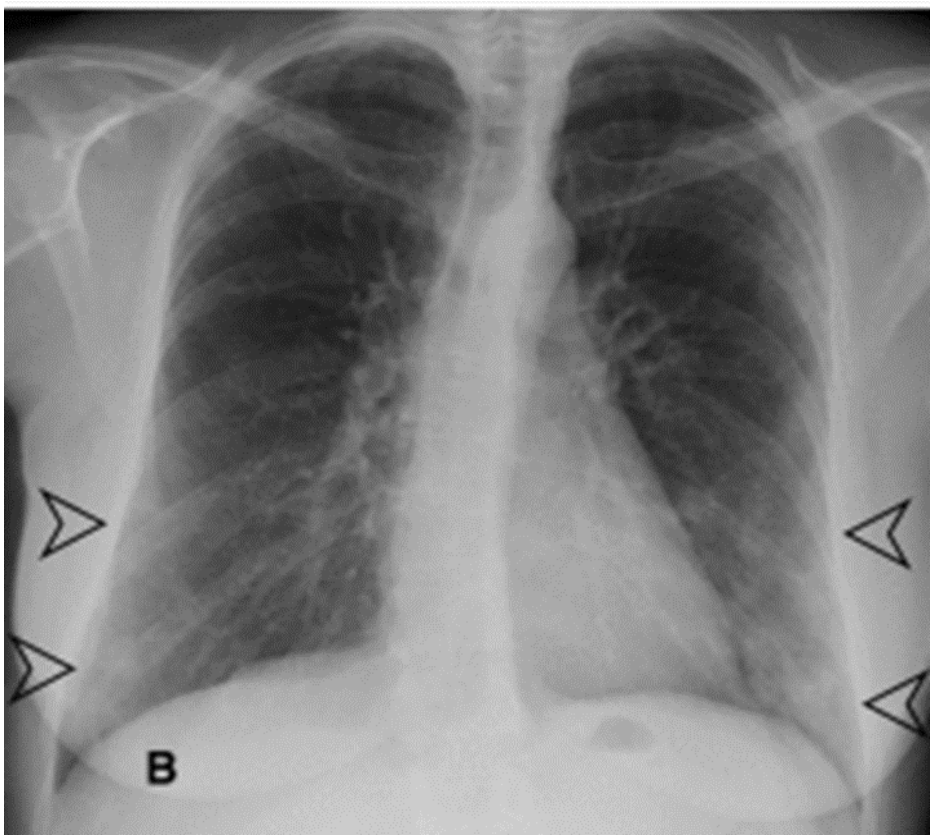


Figure 7:Bilateral areas of ground glass opacity, both less than 50%. The score given is 4 (10)

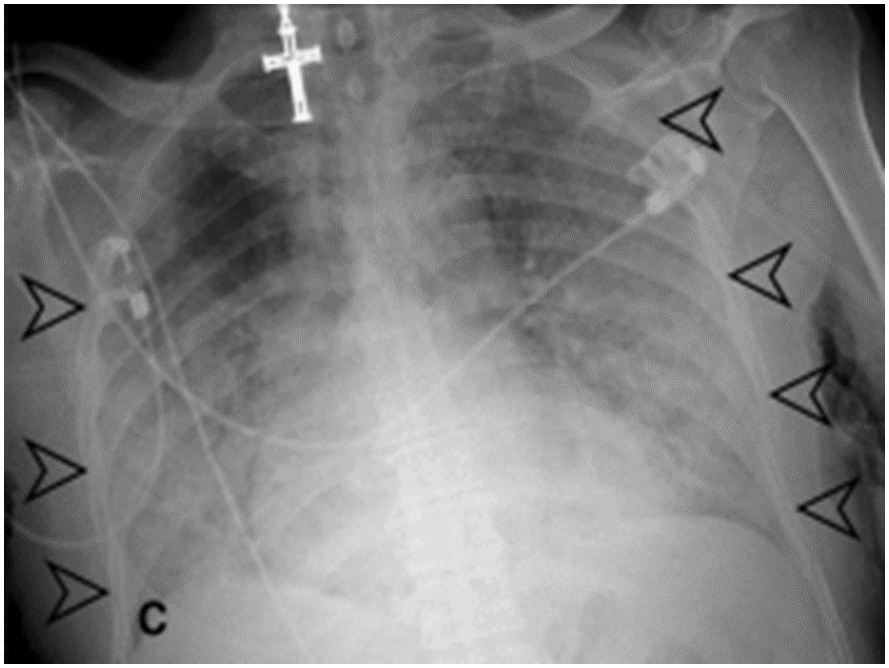


Figure 8:The right opacification was more than 50%. The left lung opacification was greater than 75%. A total score of 7 was given (10).

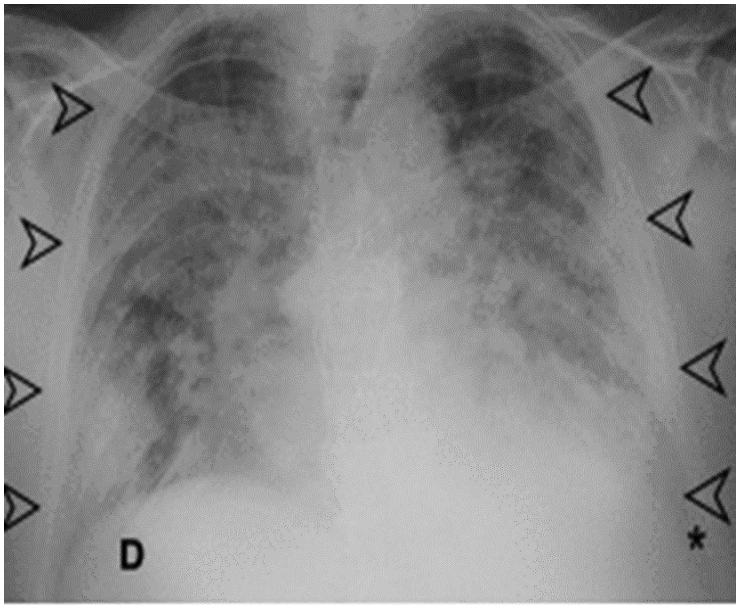


Figure 9:Bilateral areas of opacification, both involving more than 75% of the lung. The total score is 8(10).

2.10.2 The COVID-19 Scoring System

A radiographic scoring system that is particularly developed for the COVID -19 era, is named the Brixia scoring system. In this scoring system, the lung is sectioned in three zones on the frontal chest radiograph. These are indicated by letters A, B, C for the right lung and D, E, F for the left lung. The sections A and D denote the area superior to the aortic arch. The next sections B and E refer to the region bounded by the aortic arch and the lowermost portion of the inferior right pulmonary vein. Finally, C and F are for the pulmonary regions found below the inferior right pulmonary vein. A score of 0 to 3 points is deployed to each region based on the following characteristics: 0- Normal 1- to denote interstitial infiltrates 2-For alveolar and interstitial infiltrates with an interstitial pattern mostly seen 3-interstitial and alveolar infiltrates with a predominance in the alveolar presentation(8). The severity score is the sum of the scores individually given to each region. The highest severity score that can be given is 18.

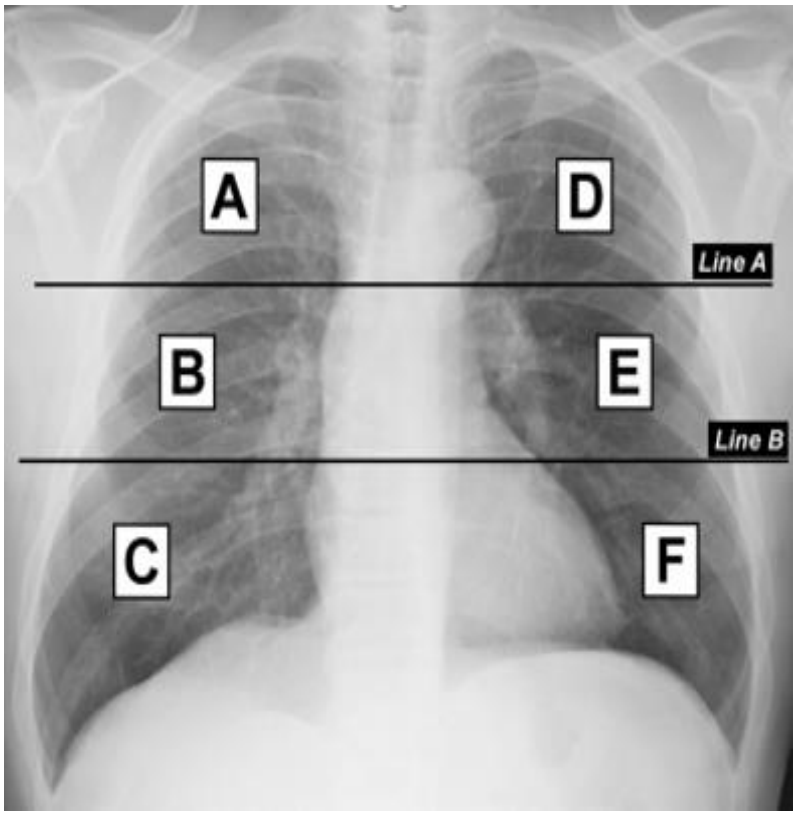


Figure 10:Lung divisions in the Brixia score scoring system(8)

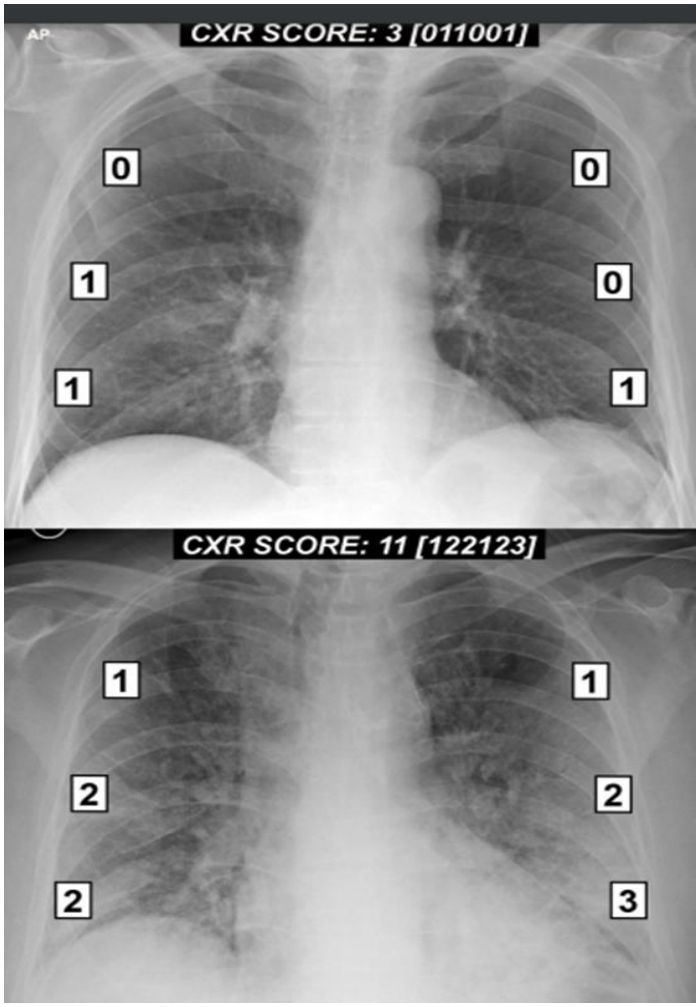


Figure 11:Illustrations of chest X-ray scores in the Brixia score scoring system(8)

2.11 Structured Chest Radiograph Reporting Template For COVID-19

In the structured chest radiograph reporting template proposed by Yates *et al*, the chest radiographic findings are categorized into five groups (43). The five categories are as follows: Negative, Atypical, Indeterminate, High Suspicion and Characteristic. According to Yates *et al*, a characteristic chest radiograph should have peripheral large multifocal opacities that are roughly of the same size. A High Suspicion chest radiographic pattern entails a large peripheral opacity confined to one lung or bilateral ground glass opacities primarily affecting the lower zones(43).

An Indeterminate chest radiographic pattern entails multiple opacities found in multiple zones of the same lung. In indeterminate chest radiographs, a pre-existing pulmonary condition may preclude the accurate interpretation of a radiograph. An artefact could similarly affect the evaluation of radiographs in this radiographic pattern. An Unlikely chest radiograph presents

with characteristic patterns of other pathologies such as pneumothorax and lobar pneumonia. A Normal chest radiograph presents no lung pathologies or no interval changes in cases of known pre- existing pulmonary or cardiac conditions. In the structured chest radiograph reporting template by Yates *et al*, the words "atypical" and "unlikely" have been used interchangeably to denote the same radiographic pattern (43).

Table 1:Chest radiographic patterns of COVID-19

Characteristic pattern	Bilateral subpleural opacities that are of large volume (>20% of lung) and predominantly affect the outer 1/3 of the lung High confidence that the opacities are not artefactual and related to the Chest wall
High Suspicion pattern	Unilateral subpleural opacity that are of large volume (>20% of lung). Bilateral large volume patchy or ill-defined opacities No apical predominance No perihilar distribution Do not fit the characteristic pattern High confidence that the opacities are not artefactual and related to the Chest wall
Indeterminate pattern	Unilateral large volume patchy or multilobar opacities Unilateral or bilateral small volume opacity (<20% of lung) Suspected superimposed opacity overlying significant underlying parenchymal disease which may limit evaluation for acute disease Difficulty distinguishing a peripheral opacity from an artefact related to the chest wall
Unlikely Pattern	Pleural effusion Heart failure pattern Apical predominance Lobar pneumonia Cavitation Pulmonary nodule/mass
Normal pattern	Normal lungs on Chest X-ray No definitive interval change if there is a long-standing chronic finding

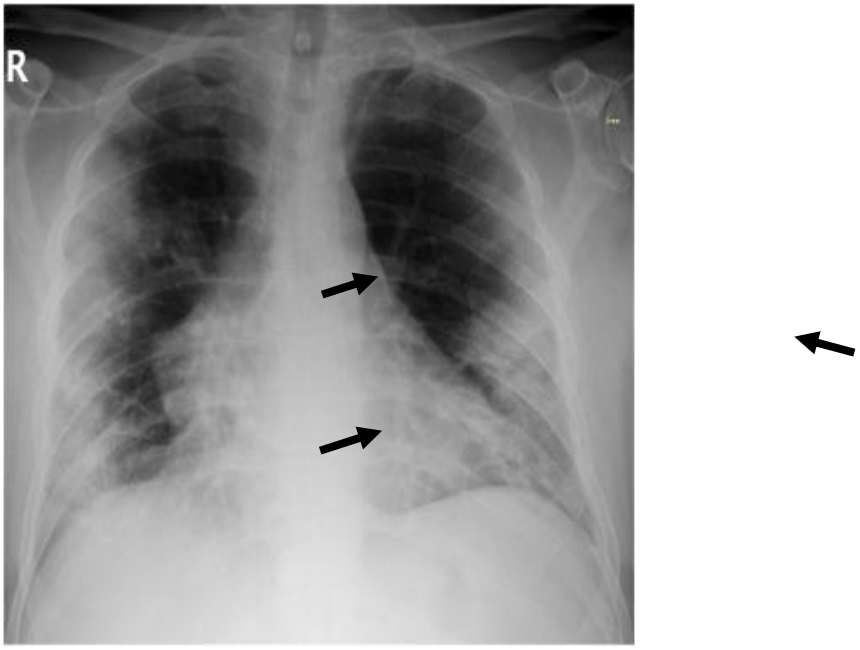


Figure 12:Bilateral peripheral multifocal opacities demonstrated in the characteristic chest radiograph(43)

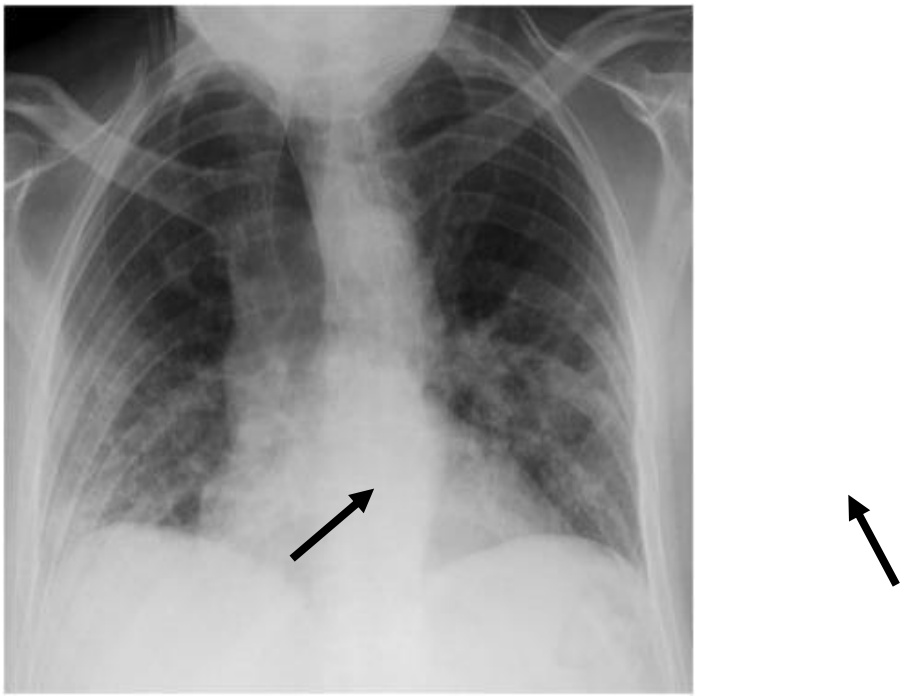


Figure 13:Bilateral lower zone patchy opacities seen in the high suspicious pattern(43)

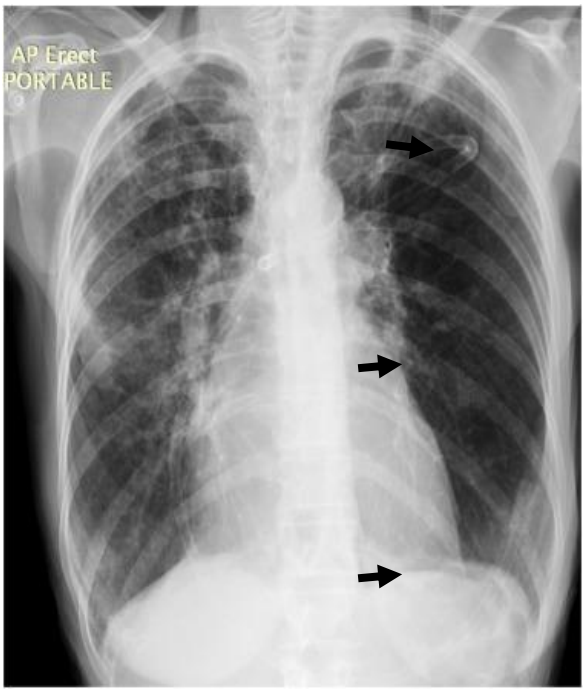


Figure 14:Right lung multilobar opacities seen in a patient with chronic obstructive pulmonary disease, in this indeterminate pattern chest radiograph (43)

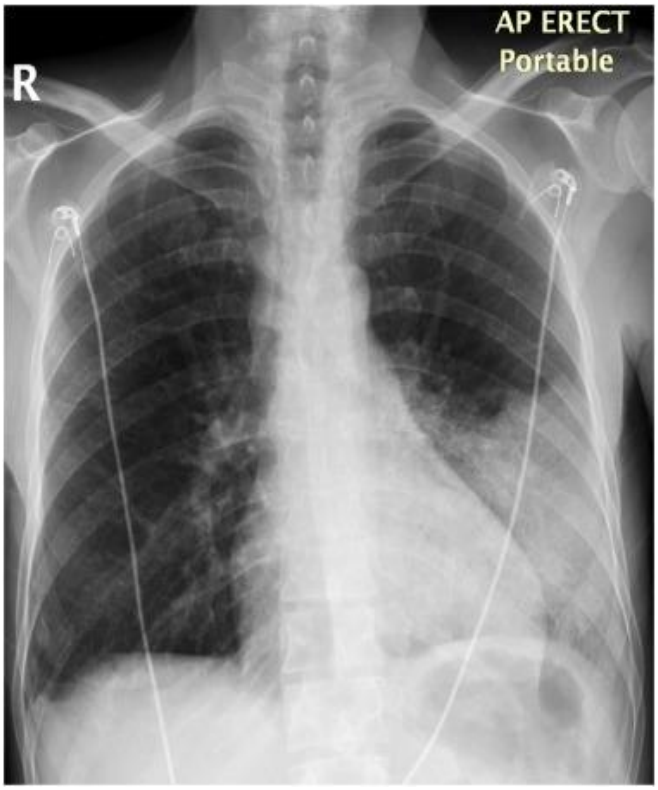


Figure 15:Left lower zone consolidation suggestive of lobar pneumonia- in this unlikely pattern chest radiograph (43).

2.12 The 4 Categories of the COVID-19 Chest Radiograph

The British Society of Thoracic imaging structured a COVID-19 reporting template for quality assurance purposes(44). The template categorizes chest radiographs into four groups: Normal, classic, indeterminate and non-COVID-19.

Table 2:The 4 Categories of the COVID-19 Chest Radiograph

NORMAL	COVID-19 not excluded, please correlate with PCR
CLASSIC/PROBABLE COVID-19	Lower lobe and peripheral predominant multiple opacities that are bilateral (>> unilateral)
INDETERMINATE FOR COVID-19	Does not fit Classic or Non-COVID-19 descriptors" or "poor quality film
NON -COVID-19	Pneumothorax/lobar pneumonia/pleural effusion(s)/pulmonary oedema/other

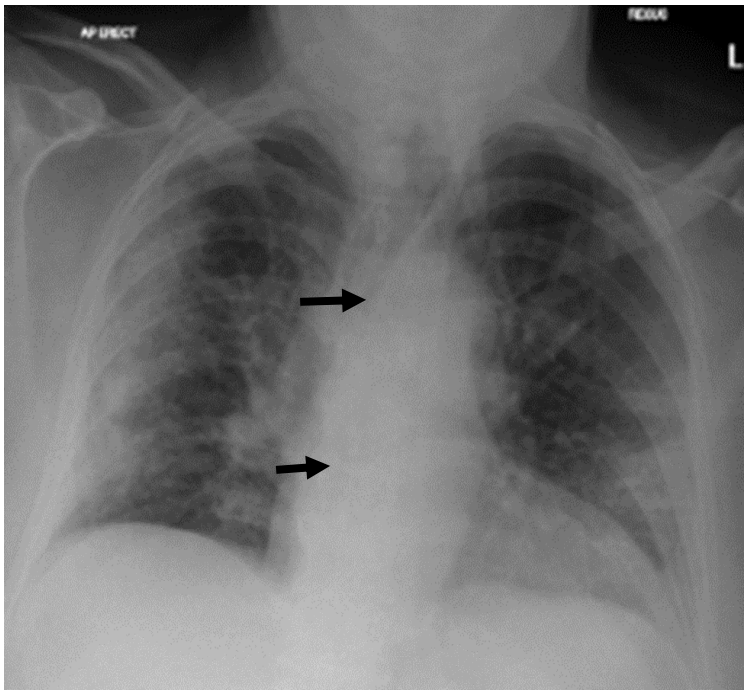


Figure 16:A frontal radiograph demonstrating the classic pattern of bilateral peripheral opacities (44).

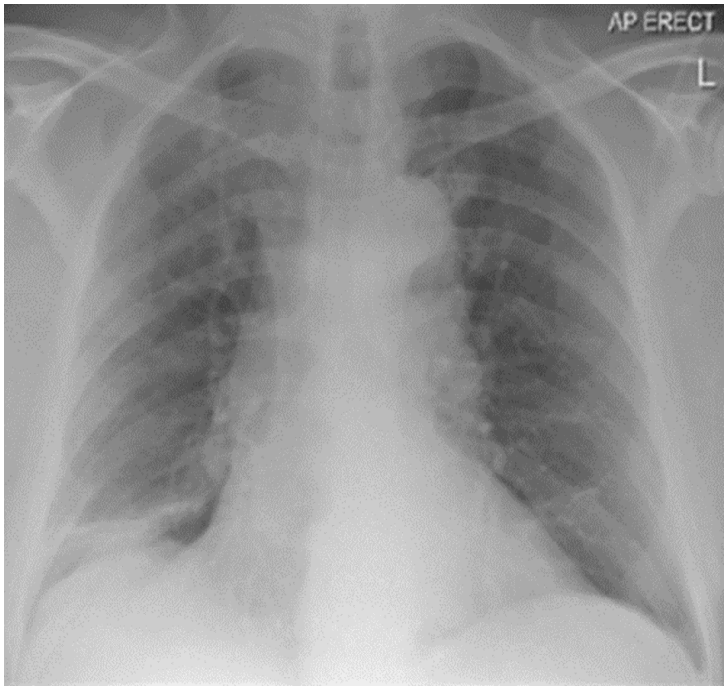


Figure 17:A chest radiograph typical of the indeterminate pattern(44).

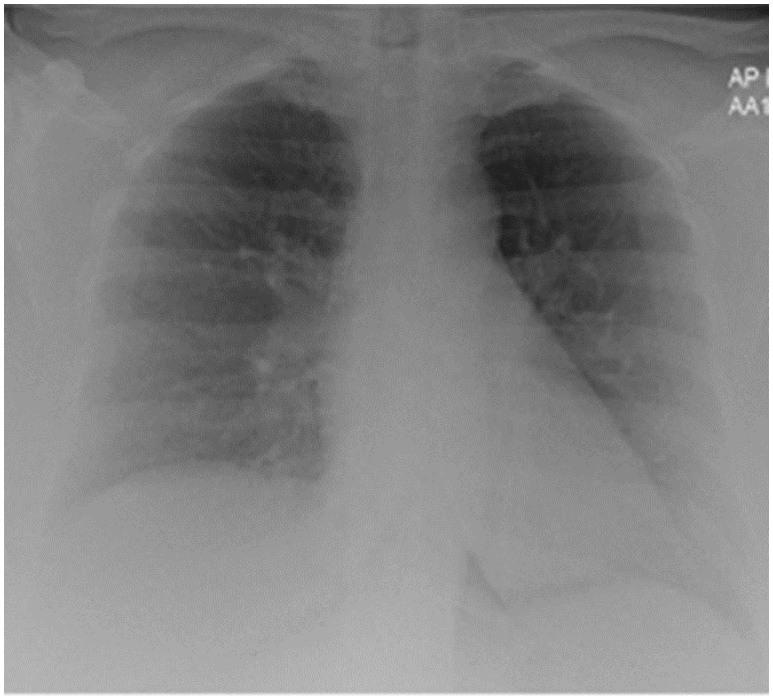


Figure 18:A frontal radiograph categorized in the "Normal" pattern(44).

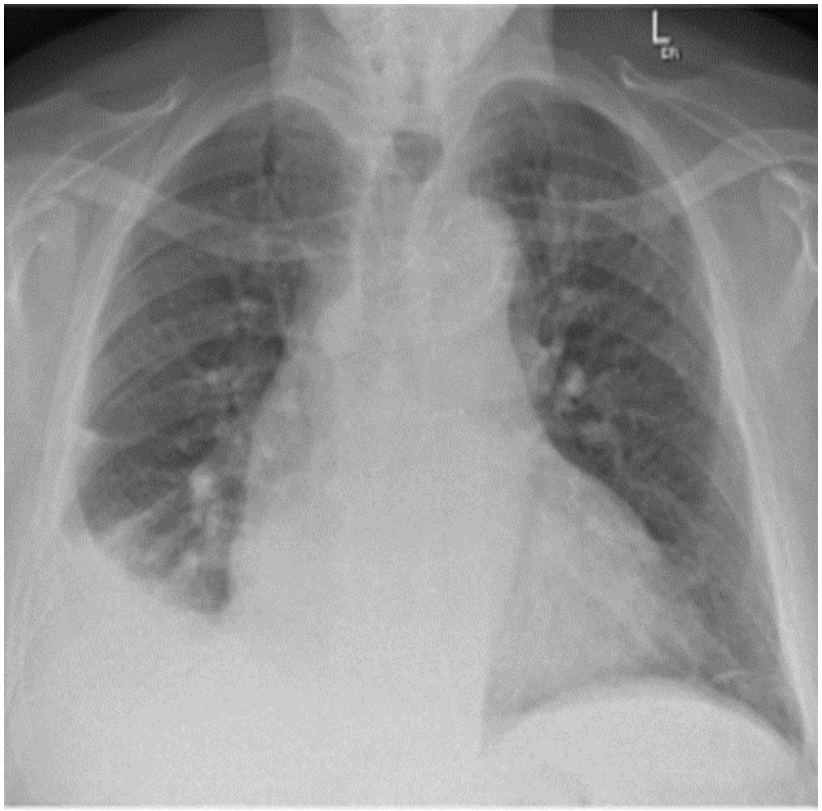


Figure 19:A frontal radiograph demonstrating the "non-COVID" pattern (44).

2.13 Biomarkers Associated With COVID-19 Disease Progression

Several biomarkers have been identified to assess the disease progression among COVID-19 patients. These biomarkers also play a role in risk stratification predicting those patients who would develop severe illness (42). These biomarkers consist of hematological parameters such as lymphocyte count, neutrophil count, platelet count and haemoglobin (45).They also include inflammatory biomarkers such as C-reactive protein, D-dimer and lactate dehydrogenase (45). In the haematological biomarkers, the neutrophil count was increased in patients with COVID-19, conversely the lymphocyte count was markedly reduced (45).

Therefore, in the general assessment of the white blood cell count in COVID-19 patients, the neutrophil to lymphocyte ratio (NLR) was elevated (45).Studies have also demonstrated a significant inverse relationship between the lymphocyte count and chest radiographic scores among COVID-19 patients (42). The platelet counts of patients with COVID-19 are reduced (45).Low platelet counts in COVID-19 patients are associated with increased risk of mortality (45). The COVID-19 patients presenting with low platelet counts were at an increased risk of developing respiratory distress and therefore requiring oxygen supplementation(42). The

haemoglobin levels were reduced in COVID-19 patients (42).These patients with low haemoglobin levels were at risk of severe COVID-19 illness and increased mortality (42,46)
The C-reactive protein (CRP) levels were elevated among COVID-19 patients (45). Similarly, the lactate dehydrogenase levels are elevated among COVID-19 patients (42,45).Studies have demonstrated a significant positive correlation between the levels of C-reactive protein and chest radiographic scores (42,47).
A direction correlation has also been established between the lactate dehydrogenase levels and chest radiographic scores (42,47).
Pulse oximetry is an non-invasive approach in the assessment of oxygen levels (48).The oxygen levels also known as oxygen saturation (SpO_2), are considered normal when they are above 95% (48). Pulse oximetry has therefore been utilized as an invaluable biomarker in managing COVID-19 patients with respiratory symptoms (49).Studies have shown a negative correlation between the levels of oxygen saturation (SpO_2) and chest radiographic scores (42). In a study by Hui *et al*, the chest radiographic scores were a better predictor for the need of supplemental oxygen among COVID-19 patients, than the levels of the laboratory biomarkers(42).

2.14 Fundamentals of Chest Radiography

The chest radiograph is the most commonly requested radiologic examination. It is often requested as a first-line investigation in clinical practice. X-rays are a type of electromagnetic radiation that exhibit high-frequency short wavelength. They have the ability to penetrate different body tissues to differing extents(50).
Chest radiography is a simple examination and it is widely available. The time acquisition in chest radiography is very short. It is also a relatively cost-effective imaging modality. Chest radiography relies on the inherent natural contrast in the patients subject to the radiographic examination. This further adds to its simplicity as it requires no contrast administration. Due to short acquisition times and its availability, the chest radiographic examination can be carried out on majority of patients presenting with respiratory complaints. As a primary investigation tool for COVID-19, the chest radiograph is therefore much preferred.
The elements of image production of radiographs are similar to those seen in photography (50). Structures that are permissive to the X-ray beam tend to appear dark/black on the film, whilst structures that attenuate and absorb the X-ray beam have the opposite appearance of white on the film. Thus, this differential intensity in the way structures interact with the X-ray beam is termed as subject contrast (51).

2.15 Limitations of Chest Radiography

There is an increased likelihood of using portable chest radiography and AP views in imaging COVID-19 patients, as most admitted COVID-19 patients are critically ill(52). Furthermore, portable radiography is ideal to prevent cross-infection in the radiological units(52,53). The lower quality of AP images from portable chest radiography makes them difficult to interpret(54). This is mostly attributed to the posture in AP radiographs that limits full inspiration. The poor inspiratory effort is also partially attributed to the patient's own lung pathologies that can significantly inhibit full inspiration. In light of the inferior quality of the AP chest radiographs, lung pathologies may appear more severe and pneumonic processes can be overlooked. The cardiac outline also appears much larger in AP radiographs.

3.0 CHAPTER THREE: STUDY JUSTIFICATION & METHODOLOGY

3.1 Study Justification

Chest radiography is typically the first imaging investigation obtained in the diagnostic workup of patients with COVID-19 given its portability, wide availability, speed, and low costs. Kaleemi *et al* used the modified RALE score to evaluate chest radiographs at admission. They demonstrated a positive correlation between the highest chest radiographic scores and in-hospital mortality among COVID-19 patients(11). Similarly, Reeves et al showed that the highest chest radiographic scores at admission were positively correlated to in-hospital mortality (14).Therefore, the chest radiograph obtained at the onset of the hospital admission is not only essential in the assessment of the degree of pulmonary disease but also has a prognostic value in the management of COVID-19 disease.

This study purposed to correlate the chest radiographic scores at admission to the in-hospital mortality of RT-PCR confirmed COVID-19 patients. This is with the aim of utilizing the chest radiographic scores at admission as early prognostic indicators in the management of COVID-19 patients.

Considering that Kenya is a resource limited setting, an early risk assessment of patients' mortality will allow physicians to triage patients and prioritize resources from the outset of patients' hospital course.

No local studies have been done that correlate the chest radiographic scores at admission with the in-hospital mortality of RT-PCR confirmed COVID-19 patients.

3.2 Research Question

What is the correlation of the chest radiographic scores at admission to the mortality of COVID-19 patients at the Kenyatta National Hospital?

3.3 Study Objectives

3.3.1 Broad Objective

To correlate the chest radiographic scores at admission to the in-hospital mortality of COVID-19 patients

3.3.2 Specific Objectives

a) To determine the demographic characteristics of admitted RT-PCR positive COVID-19 patients

b) To score the chest radiographs at admission in accordance with the modified RALE score
c) To correlate the chest radiographic scores at admission to the in-hospital mortality of COVID-19 patients

3.4 Methodology

3.4.1 Study Design

A retrospective cross-sectional study

3.4.2 Study Duration

Over a period of 12 months from 1st May 2020 to 31st April 2021.

3.4.3 Study Area Description

The chest radiographs were obtained from the Radiology Department at the Kenyatta National Hospital. The patients' medical records were obtained from the Health Information department at the Kenyatta National Hospital.

3.4.4 Sampling Method

Sequential non-probability sampling within a predetermined time period

3.4.5 Study Population

Admitted RT-PCR confirmed COVID-19 patients with AP(Antero-posterior) or PA (Postero-Anterior) chest radiographs done at the onset of their admission.

3.4.6 Inclusion Criteria

- Patients more than 18 years of age
- Patients who had undergone a confirmatory reverse transcriptase polymerase chain reaction (RT-PCR) test for COVID-19.
- Patients who had a chest radiograph done at admission

3.4.7 Exclusion Criteria

- Patients under the age of 18 years
- RT-PCR confirmed COVID-19 patients without chest radiographs done at admission

3.5 Sample Size Determination

Sample size was calculated using the formula below (55)

$$n = \frac{Z^2 x\ P(1-P)}{d^2}$$

Where,

n = Desired sample size

Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P = expected true proportion (estimated at 80.0%, from a retrospective study conducted by Cristian GM. et al (2020) who retrospectively reviewed clinical and imaging records of all patients referred to the emergency department at two institutions for suspected SARS-CoV-2 infection between February 22 and April 8, 2020; found 80.0% of them had a chest X-ray severity score of between 13-16.)(56)

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.80(1-0.80)}{0.05^2} = 246$$

A Sample size of 246 patients will be required for the study.

3.6 Variables

3.6.1 Demographic characteristics:

- age
- sex

3.6.2 Co-morbidities

- Cardiac disease
- Hypertension
- Diabetes
- Obesity
- Smoking history

3.6.3 Presenting Complaints

- Fever
- Cough
- Rhinitis

- Dyspnea
- Myalgias
- Conjunctivitis
- Headache
- Nausea
- Vomiting
- Diarrhea

3.6.4 Modified RALE Score

- 1 – less than 25% lung involvement
- 2 – 25% to 50% lung involvement
- 3 – 50% to 75% lung involvement
- 4 more than 75% lung involvement

3.6.5 Clinical outcome

- In hospital mortality
- Discharged

3.7 COVID-19 Infection Protocols

In instances of close proximity interactions with patients infected with COVID-19, such as in undertaking portable chest radiography in the isolation wards, strict protective measures were advised. These measures included: the use of disposable head gear, the wearing of N95 masks, the use of eye shields in the form of goggles or screens, the use of latex hand gloves and the wearing of protective disposable gowns(54). Furthermore, shoe or boot covers were equally advised to enhance protection (54). The healthcare workers who worked far away from infected COVID-19 patients were only required to don disposable surgical masks and their regular working clothes (54). They were also advised to maintain social distance. The implementation of strict hand hygiene protocols was advised for all healthcare workers (54).

3.8 Data Collection Procedures

A structured data collection form was used to collect the data. The patients were identified by only their hospital numbers, X-ray numbers and their initials on the data collection form. Demographic characteristics and clinical information were obtained from the patients' medical records archived at the Health Information department. The chest radiographs were obtained from the archives at the Radiology department and they were stored in a CD. The CD had a

very strong password that was available only to the principal investigator. Chest radiographic findings on the chest X-ray films were reviewed independently by the primary investigator and were subsequently verified by the supervisor consultant radiologists.

3.9 Quality Assurance Procedures

Only chest radiographs of adequate diagnostic quality were used in the study. Quality control was also applied in the study by ensuring that the chest radiographic findings were reproducible by engaging at least 3 independent readers for the examinations under study. The readers were the principal investigator and the supervisors. Findings between the two independent readers were analysed for any variations and consistency. Use of standardized data collection forms ensured reliability of results.

3.10 Ethical Considerations

The study was conducted after approval by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON – ERC). A consent waiver was sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON – ERC). This was in light of the retrospective nature of the study, making it difficult to obtain an informed consent from most of the patients who would have been discharged from the care of the Kenyatta National Hospital. Furthermore, the study involved the interpretation of chest radiographs obtained from the archives of the Radiology department at the Kenyatta National Hospital with correlation obtained from medical records archived at the Health Information department. No new chest radiographic examinations were performed on the patients; therefore, patients were not subjected to further radiation exposure. Permission to conduct the study was approved by the Kenyatta National Hospital Administration. The information obtained from the study was held in utmost confidence. In order to safeguard the patient's privacy, only hospital numbers, X-ray numbers and patients' initials were used for identification. The information obtained from the study was stored in a database under a very strong password that was available only to the principal investigator.

3.11 Data Management

The information collected was entered and analysed in SPSS version 23.0. The variables analysed included demographics, presenting complaints, comorbidities, the scores of the chest radiographic findings and the clinical outcomes. Analysis of data was done using descriptive and inferential statistics.

The demographic data was analysed and presented as frequencies and proportions for categorical data or as means with standard deviations for continuous data. Presenting complaints and chest radiographic scores were presented as frequencies and proportions. Correlation of chest radiographic scores and in-hospital mortality was done with the use of chi-square tests, t-tests or ANOVA where applicable. All statistical tests were considered to be significant where the $p < 0.05$.

3.12 Dissemination of study findings

The findings of the study will be disseminated to the University of Nairobi and Kenyatta National Hospital departments of Radiology and the Kenyatta National Hospital Infectious Diseases department. The findings will also be disseminated to the medical library of the University of Nairobi. The findings will be published in peer reviewed open access journals.

4.0 CHAPTER FOUR: RESULTS

4.1 Demographic Characteristics and Comorbidities

A total of 246 RT-PCR positive COVID-19 patients were included in this study. Out of the 246 patients 147 were males (59.8%) while 99 were female (40.2 %) giving a male: female ratio of 1.5:1. Results of the demographic characteristics indicate that majority of the respondents (96, 39%) were aged above 50.0 years. The mean age was 47.6 (SD 14.3) years, the median age of the patients was 47.0 (IQR 37.0 – 57.0) years and the minimum and maximum age being 18.0 years and 87.0 years respectively. This is illustrated in table 3.

Table 3:Demographic characteristics

		Frequency *(n=246)*	**Percent**
Age	≤30	32	13.0
	31 – 40	50	20.3
	41 – 50	68	27.6
	>50	96	39.0
Gender	Male	147	59.8
	Female	99	40.2

Out of the 246 patients, 110 (44.7%) of the patients had one or more comorbidity. The leading comorbidities among the patients was diabetes (62, 56.4%), and hypertension (54, 49.1%) as seen in table 4

Table 4:Comorbidities

	Frequency	**Percent of patients *(n=110)***
Hypertension	54	49.1%
Diabetes	62	56.4%
Cardiac disease	13	11.8%
HIV	8	7.3%
TB	4	3.6%
Cancer	6	5.5%
Breast cancer	2	1.8%
Asthma	3	2.7%
CKD	2	1.8%

4.2 Presenting Complaints

Out of the 246 patients, 244 (99.2%) of the patients presented with one or more complaints, of which the top complaints were cough from 185 (75.8%) and dyspnea from 136 (55.7%) as illustrated on table 5.

Table 5:Presenting Complaints

	Frequency	**Percent of patients *(n=244)***
Fever	51	20.9%
Cough	185	75.8%
Dyspnea	136	55.7%
Rhinitis	6	2.5%
Myalgia	29	11.9%
Headache	17	7.0%
Vomiting	2	0.8%
Diarrhea	2	0.8%

4.3 Modified RALE score

Out of the 246 admission chest radiographs evaluated in this study, 106 (43.1%) were normal chest radiographs. The remaining, 140 chest radiographs demonstrated positive findings of which (64, 26%) chest radiographs demonstrated a Modified RALE score of (1-4) and (76, 30.9%) chest radiographs had a score of (5-8). These proportions were not statistically significant (p value=0.231). This is demonstrated on table 6. The highest chest radiographic score showed no statistically significant preference for a particular lung side (p value 0.15).

Table 6:Modified RALE score

Score	**Frequency**	**Percent**
0	106	43.1
1	10	4.1
2	15	6.1
3	19	7.7
4	20	8.1
5	15	6.1
6	14	5.7
7	18	7.3
8	29	11.8

Table 7:Lungs

Score	**Right,** *n (%)*	**Left,** *n (%)*	**p-value**
0	115 (46.7)	131 (53.3)	0.149
1	15 (6.1)	20 (8.1)	0.381
2	32 (13.0)	26 (10.6)	0.402
3	36 (14.6)	33 (13.4)	0.697
4	48 (19.5)	36 (14.6)	0.150

4.4 Clinical Outcomes

Out of the 246 patients evaluated in this study, 215 (87.4 %) patients were discharged while 31(12.6%) patients were in-hospital mortalities. This is illustrated on table 8. The mean age of the in-hospital mortalities was 55.3±17.4 whereas the mean age of the discharged patients was 46.5±13.5. This was statistically significant at a p value of 0.011 as seen on Table 8. Out of the 31 in-hospital mortalities 21 (67.7%) were male whereas 10 (32.3%) were female which was not statically significant at p value 0.332. Out of the discharged 215 patients, 126 (58.6 %) were male whereas 89 (41.4%) were female and was statistically insignificant.

Table 8:Clinical Outcomes

	Frequency	**Percent**
In-hospital mortality	31	12.6
Discharged	215	87.4

P value = 0.001

Table 9:Demographic characteristics and Mortality

		Dead	**Alive**	**p-value**
Age, *mean±SD*		55.3±17.4	46.5±13.5	**0.011**
Gender, *n (%)*	Male	21 (67.7)	126 (58.6)	0.332
	Female	10 (32.3)	89 (41.4)	

4.5 Correlation of Comorbidities and The In-Hospital Mortality Of COVID-19 Patients

No specific underlying comorbidity was associated with an increased risk of in-hospital mortality. Cochran-Armitage (Chi-square test for trend) test was used to assess if there was an association between the increasing number of comorbidities and mortality. There was no statistical association.

Table 10:Comorbidities and Mortality

		Dead, *n (%)*	**Alive,** *n (%)*	**p-value**
Comorbidity	Yes	17 (54.8)	93 (43.3)	0.225
	No	14 (45.2)	122 (56.7)	
Diabetes	Yes	8 (25.8)	54 (25.1)	0.934
	No	23 (74.2)	161 (74.9)	
HTN	Yes	8 (25.8)	46 (21.4)	0.579
	No	23 (74.2)	169 (78.6)	
Cancer	Yes	2 (6.5)	6 (2.8)	0.283
	No	29 (93.5)	209 (97.2)	
Cardiac	Yes	2 (6.5)	11 (5.1)	0.756
	No	29 (93.5)	204 (94.9)	
CKD	Yes	0 (0.0)	2 (0.9)	0.590
	No	31 (100.0)	213 (99.1)	
HIV	Yes	3 (9.7)	5 (2.3)	0.066
	No	28 (90.3)	210 (97.7)	
TB	Yes	1 (3.2)	3 (1.4)	0.419
	No	30 (96.8)	212 (98.6)	
Asthma	Yes	0 (0.0)	3 (1.4)	1.000
	No	31 (100.0)	212 (98.6)	

Table 11:Number of Comorbidities and Mortality

		Dead, *n (%)*	**Alive,** *n (%)*	**p-value**
Number	0	14 (10.3)	122 (89.7)	0.273
	1	10 (14.5)	59 (85.5)	
	2	7 (18.4)	31 (81.6)	
	3	0 (0.0)	3 (100.0)	

4.6 Correlation of Presenting Complaints and In-Hospital Mortality

There was increased risk of in-hospital mortality among patients who presented with dyspnea.

Table 12:Presenting symptoms and Mortality

		Dead, *n (%)*	**Alive,** *n (%)*	**p-value**
Fever	Yes	9 (29.0)	42 (19.5)	0.223
	No	22 (71.0)	173 (80.5)	
Cough	Yes	22 (71.0)	163 (75.8)	0.559
	No	9 (29.0)	52 (24.2)	
Dyspnea	Yes	23 (74.2)	113 (52.6)	**0.024**
	No	8 (25.8)	102 (47.4)	
Headache	Yes	0 (0.0)	16 (7.4)	0.234
	No	31 (100.0)	199 (92.6)	
Rhinitis	Yes	0 (0.0)	6 (2.8)	1.000
	No	31 (100.0)	209 (97.2)	
Myalgia	Yes	6 (19.4)	23 (10.7)	0.227
	No	25 (80.6)	192 (89.3)	
Vomiting	Yes	0 (0.0)	2 (0.9)	1.000
	No	31 (100.0)	213 (99.1)	
Diarrhea	Yes	0 (0.0)	2 (0.9)	1.000
	No	31 (100.0)	213 (99.1)	

4.7 Correlation of RALE Score and Gender

Cochran-Armitage (Chi-square test for trend) test was used to assess if there was an association between the increasing RALE score and gender. There was no statistical association (Table 13).

Table 13:RALE score and Gender

		Male, *n (%)*	**Female,** *n (%)*	**p-value**
Number	0	60 (56.6)	46 (43.4)	0.413
	1	6 (60.0)	4 (40.0)	
	2	10 (66.7)	5 (33.3)	
	3	10 (52.6)	9 (47.4)	
	4	13 (65.0)	7 (35.0)	
	5	9 (60.0)	6 (40.0)	
	6	10 (71.4)	4 (28.6)	
	7	11 (61.1)	7 (38.9)	
	8	18 (62.1)	11 (37.9)	

4.8 Correlation of RALE Score with In-Hospital Mortality

Cochran-Armitage (Chi-square test for trend) test was used to assess if there was an association between the admission modified RALE score and mortality. There was statistical association demonstrating higher rates of in-hospital mortality among those with the highest chest radiographic scores (p value =0.001). The mean Modified RALE score of the in-hospital mortalities was also higher at 4.5±3.1, whereas the mean Modified RALE score of the discharged patients was 2.6±2.9. This is illustrated on table 14 and table 15.

Table 14:RALE score and Mortality

		Dead, *n (%)*	**Alive,** *n (%)*	**p-value**
Number	0	7 (6.6)	99 (93.4)	**0.001**
	1	2 (20.0)	8 (80.0)	
	2	0 (0.0)	15 (100.0)	
	3	2 (10.5)	17 (89.5)	
	4	3 (15.0)	17 (85.0)	
	5	2 (13.3)	13 (86.7)	
	6	3 (21.4)	11 (78.6)	
	7	5 (27.8)	13 (72.2)	
	8	7 (24.1)	22 (75.9)	

Table 15:Demographic characteristics and Mortality

		Dead	**Alive**	**p-value**
Age, *mean±SD*		55.3±17.4	46.5±13.5	**0.011**
Gender, *n (%)*	Male	21 (67.7)	126 (58.6)	0.332
	Female	10 (32.3)	89 (41.4)	
RALE, *mean±SD*		4.5±3.1	2.6±2.9	**0.001**

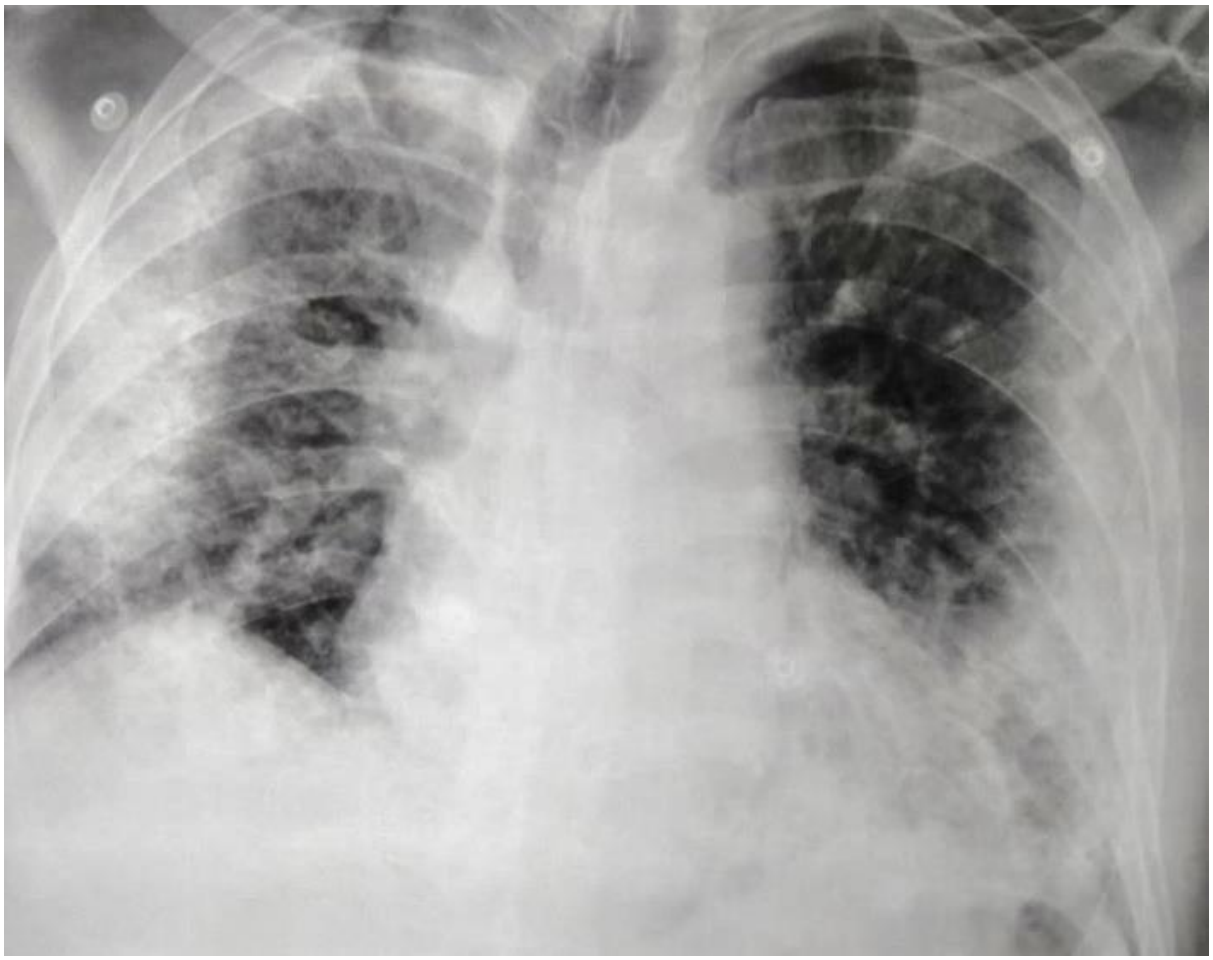
Patients with RALE scores of 7 and 8 were 4.3 (95% CI, 1.3 – 13.8, p=0.015) and 3.5 (95% CI, 1.3 – 9.7, p=0.014) times more likely to have in-hospital mortality when compared with the reference group of patients with RALE scores of between 0 to 4, and these were statistically significant.

Table 16:

		Dead	**Alive**	**OR (95 % CI)**	**p-value**
RALE Score	0 – 4	14 (53.8)	156 (81.7)	Reference	
	7	5 (19.2)	13 (6.8)	4.3 (1.3 – 13.8)	**0.015**
	8	7 (26.9)	22 (11.5)	3.5 (1.3 – 9.7)	**0.014**

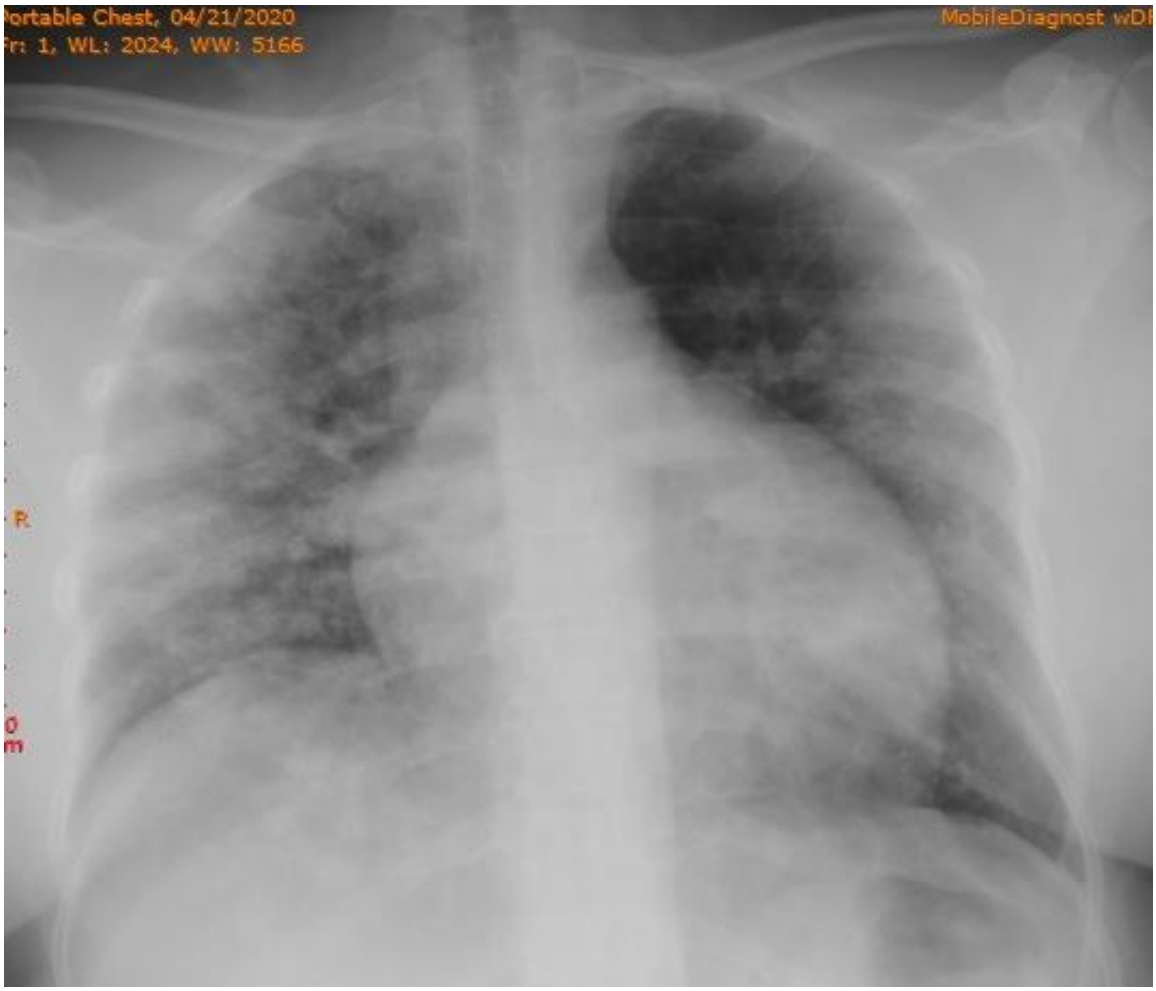
4.9 Reference cases

CASE 1



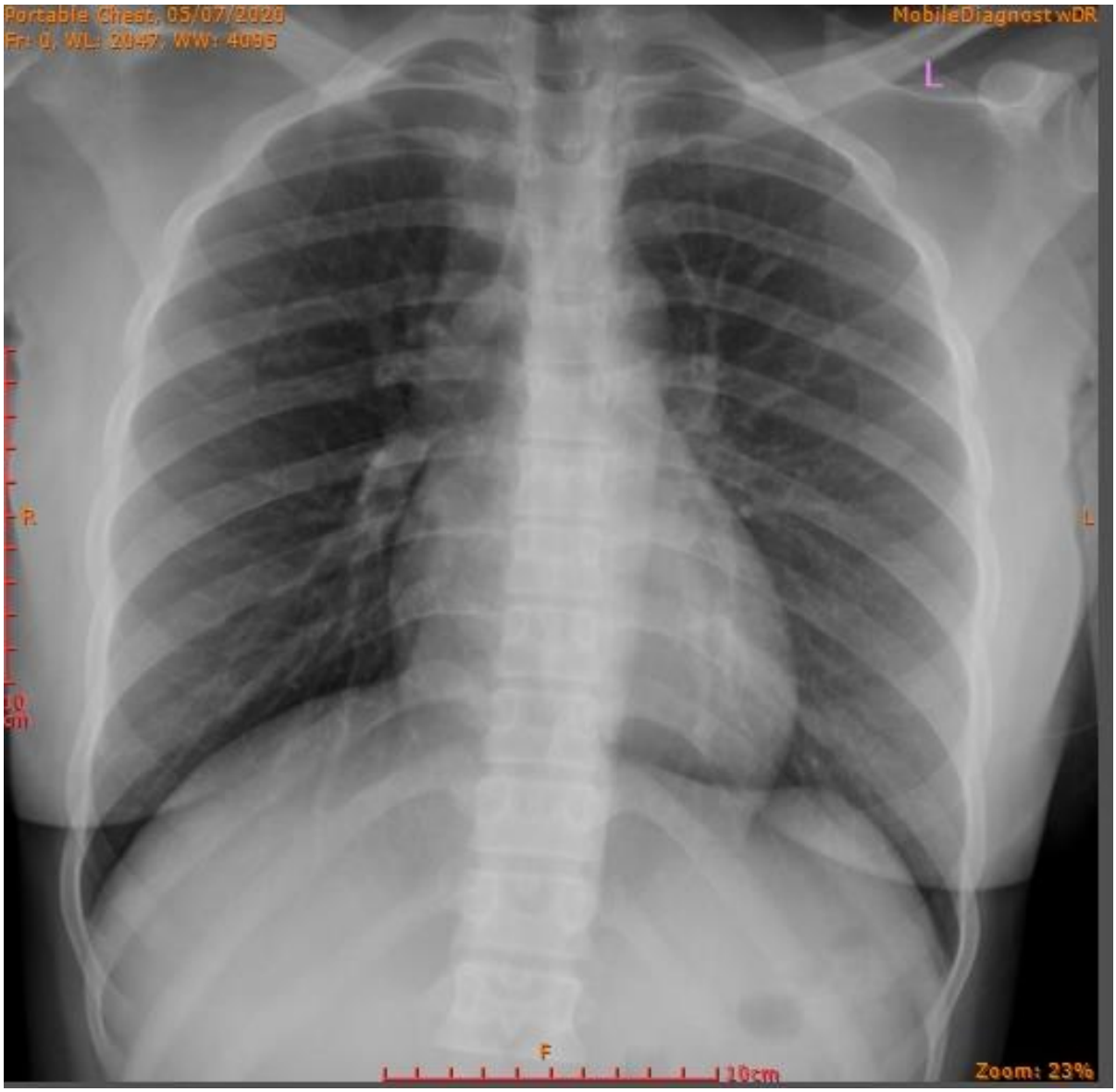
A 65-year-old RT-PCR positive male patient who presented with cough, dyspnoea and fever. The patient was a known cardiac patient. The right lung score was 4, the left lung score was 4. The total Modified RALE score was 8. The clinical outcome was in-hospital mortality.

CASE 2



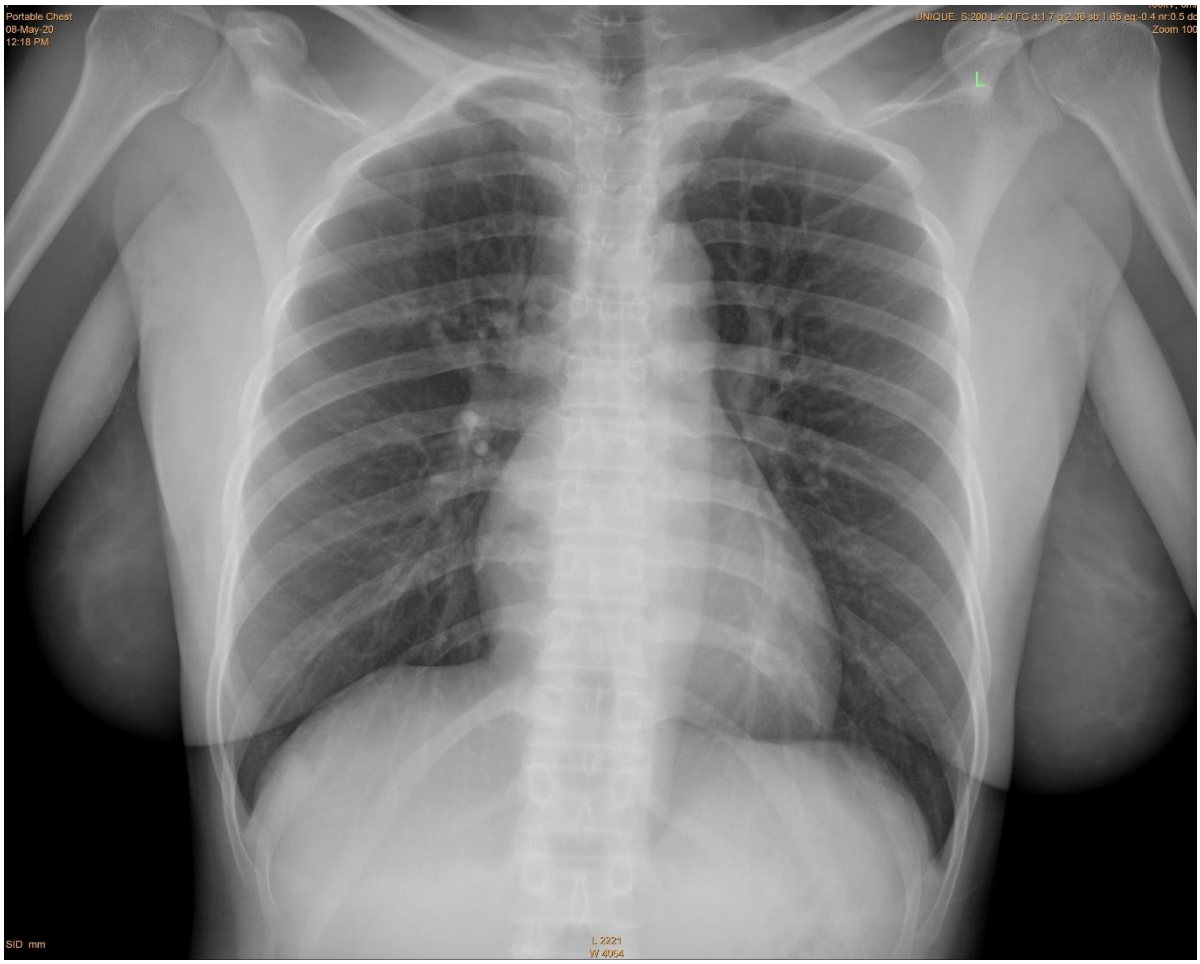
A 43-year-old RT-PCR positive female patient who is also HIV positive on antiretroviral therapy. She presented with cough and chest pain. The right lung score was 4. The left lung score was 4. The total Modified RALE score was 8. The clinical outcome was in-hospital mortality.

CASE 3



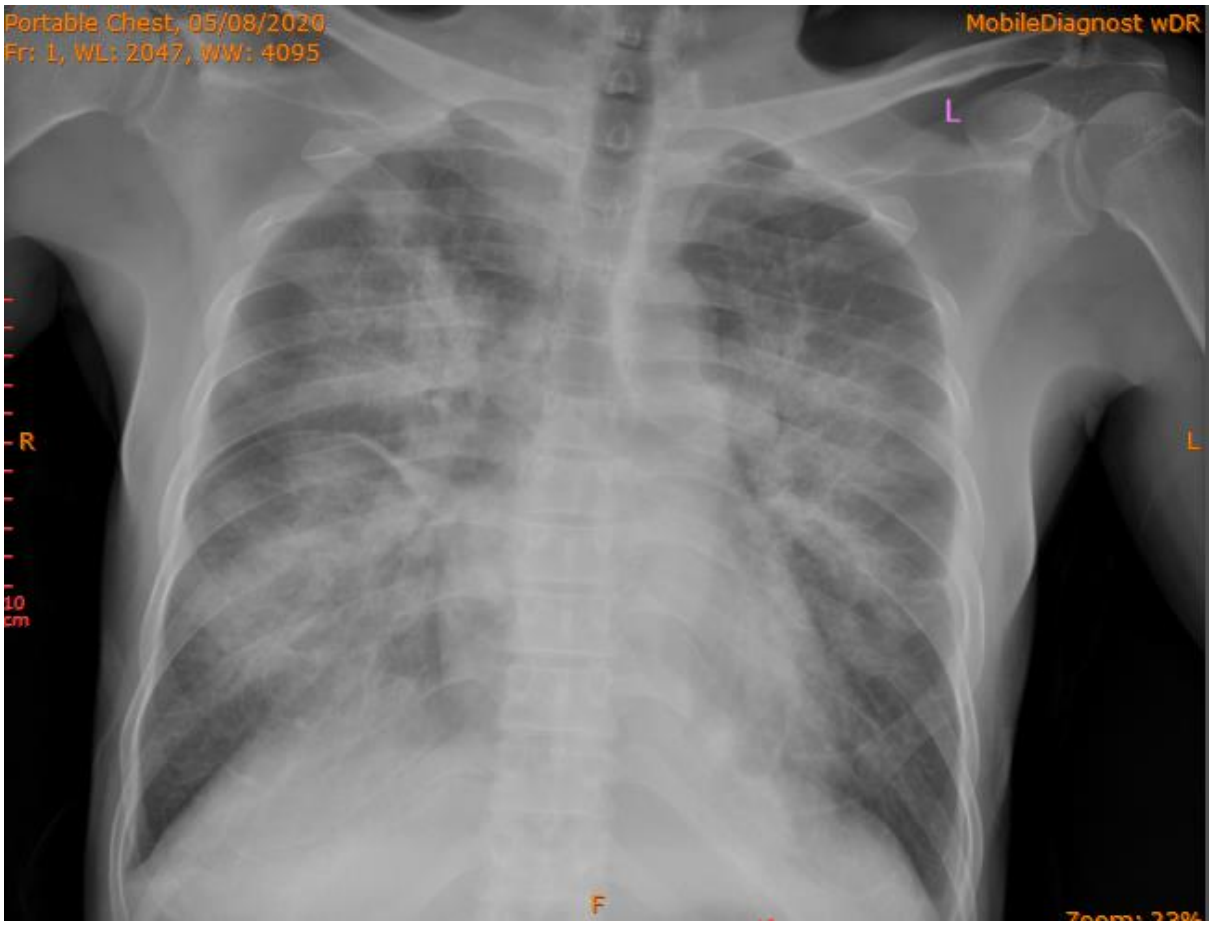
A 29-year-old RT-PCR positive female patient who presented with chest pain and difficulty in breathing. The right lung score was 0. The left lung score was 0. The clinical outcome was discharged.

CASE 4



A 40-year-old RT-PCR positive female patient who presented with fever and cough. The right lung score was 0. The left lung score was 0. The total Modified RALE score was 0. The clinical outcome was discharged.

CASE 5



A 54-year-old male RT-PCR positive patient who presented with dyspnoea, cough and chest pain. The patient was also a known asthmatic. The right lung score was 4. The left lung score was 3. The total Modified RALE score was 7. The Clinical outcome was in-hospital mortality.

5.0 CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECCOMENDATIONS

5.1 Discussion

Early prognostication in the management of COVID-19 is of outmost importance, particularly in resource-limited settings such as Kenya and Africa as a whole. Chest radiography due to its wide availability, portability and relative affordability is often the first imaging investigation performed on RT-PCR positive COVID-19 patients. This study sought to correlate the chest radiographic scores at admission among COVID-19 patients with in-hospital mortality.

The majority of the patients were males with a majority of the patients also being above the age of 50.This was similar to the characteristics of COVID-19 patients, seen in a study by Garg et al, where more than half of the admitted patients were male and more than 70% were above the age of 50 years (57).We demonstrated that 44.7 % of the patients had at least one comorbidity with diabetes and hypertension being the leading comorbidities, demonstrating a similar pattern as seen in previous studies (10,58). Our study showed no association between multiple comorbidities and increased risk of mortality to COVID-19.This was contrary to previous studies that showed an increased risk of mortality among COVID-19 patients with multiple comorbidities (59,60).The leading presenting complaints among the patients included in our study were cough and dyspnoea. Patients who presented with dyspnea were at an increased risk of mortality (p value of 0.024). Similarly in a meta-analysis of 11 studies with 2091 cases, Shi et al demonstrated a 4.34 increased likelihood of mortality in dyspneic COVID-19 (61).

The in-hospital mortality rate of the COVID-19 patients in our study was at 12.6%.This was lower than what was seen in previous studies done on the Pakistani population that demonstrated a mortality rate of 16.7% among admitted COVID-19 patients (11,62).However the mortality rate among our study population was much higher than that seen in hospitalized COVID-19 patients in Ethiopia, who demonstrated a mortality rate of 5.3% (63).Conversely, the mortality rate in our study population was much lower than the 29.7% seen among the Italian population (64). The mean age of the in-hospital mortalities was 55.3±17.4 whereas the mean age of the discharged patients was 46.5±13.5.Therefore, replicating a pattern seen in a previous study showing increased mortalities in the older COVID-19 patients (11). Among the in-hospital mortalities 67.7% were male whereas 32.3% were female, thus replicating trends seen in previous studies of increased risk of mortality among men (11,65). The factors that are

likely to explain the discrepancies in mortality based on gender include both biological and lifestyle differences(66,67). Men have been shown to have higher expression of angiotensin-converting enzyme-2 (ACE 2; receptors for coronavirus) thus providing a facilitated environment for the pathogenesis of coronavirus(66,67). The concept of sex-based immunological differences driven by sex hormones and the X chromosome, has also gained traction to explain why men are increasingly vulnerable to COVID-19 mortality(66,67). Female sex hormones such as oestrogen have been postulated to have a mitigating effect against COVID-19 mortality(66,67). Men generally demonstrate higher levels of smoking and drinking which make them more susceptible to severe COVID-19 infections(66,67). Furthermore, men demonstrated more reluctance in adhering to the COVID -19 preventive measures such as handwashing and social distancing, therefore increasing the risk of being infected with COVID-19(66,67).

We demonstrated that 43.1% of the 246 chest radiographs, had no positive chest radiographic findings and therefore scored 0 on the modified RALE score. The greatest number of chest radiographs had a score of 0. This high number of normal chest radiographs could be attributed to the acquisition of the radiographs during the early viral infection period(68). In a study by Stephanie et al, it was shown that certain ethnicities particularly, African Americans are more likely to have a higher number of false negative findings on the initial COVID-19 evaluation chest radiograph(68). The authors suggested that the chest radiographic differences based on ethnicity were likely due to differential testing -with some patients having access to testing for more mild cases and others not- or innate biological variations among the different ethnicities(68). In the same study, it was postulated that the different rates of comorbidities amongst the various ethnic groups may have contributed to different chest radiography finding severities (68).Therefore, the early acquisition of chest radiographs in our study population coupled with the comorbidity profile of our study participants, could have resulted in the high number of normal chest radiographs.

We found that the patients with modified RALE scores of 7 were 4.3 times more likely and those with scores of 8 were 3.5 times more likely to have in-hospital mortalities when compared with the reference group of patients with RALE scores of between 0 to 4. Similarly, Kaleemi et al demonstrated that the patients with Modified RALE scores 5-8 had a significantly higher mortality rate than those with scores 0-4. Kaleemi et al showed that the mortality of those with scores 5-8 was 28% while those of scores 0-4 was 11.1%, this was statistically significant at a p value of 0.008(11). Similarly, Au-Yong et al, while utilising various chest severity scoring

systems to evaluate the radiographs of COVID-19 patients, demonstrated a threefold increased risk of ICU or death associated with over 75% opacification compared to 0-25% opacification on a radiograph (69). In our study, the mean Modified RALE score of the in-hospital mortalities was also higher at 4.5±3.1, whereas the mean Modified RALE score of the discharged patients was 2.6±2.9. Similarly Kaleemi et al, demonstrated a higher mean RALE score in the mortalities than the survivors (11). A trend that was also demonstrated by Sensusiati et al, while utilising the modified RALE score to assess the radiographs of COVID-19 patients (70).

5.2 Limitations

This study faced a number of limitations, including the retrospective nature of its design and the relatively small sample size. Furthermore, there was no uniform presentation of our patients to the hospital. Some were admitted in the earlier course of their illness, while some presented much later. Therefore, the various chest radiographic findings could have been confounded by the time of their presentation to the hospital. Moreover, as portable chest radiographs were used, positioning and other exposure-related factors may confound chest radiographic findings. Finally, this study did not contain a control group of patients (COVID-19 negative) to compare chest radiographic findings and chest radiographic severity score with.

5.3 Conclusion

The modified RALE score is an important tool for the evaluation of the initial chest radiographs of COVID-19 patients. Our study has demonstrated that the modified RALE score is a reliable prognostic indicator demonstrating that patients with the highest RALE scores are at an increased risk of mortality. The modified RALE score is easily reproducible and can be rapidly used to assess the chest radiographs of COVID-19 patients. Therefore, it can be an invaluable tool in high- volume, resource constrained settings in providing rapid and objective prognostic information in the management of COVID-19 patients.

5.4 Recommendations

The findings of this study shows that the modified RALE score can be used in the reporting of the initial chest radiographs of COVID-19 patients at KNH. A larger study multi-centric study with appropriate controls can be considered to confirm if the findings are reproducible and generalizable.

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APPENDICES

Appendix A. Data Collection Form

Title: Chest radiographic scores at admission correlated to the mortality of COVID-19 patients at the Kenyatta National Hospital

Investigator: Dr. Esther C. M. Gumbe, Resident Department of Diagnostic Imaging and Radiation Medicine, University of Nairobi

DEMOGRAPHIC CHARACTERISTICS		
Patient X-ray number		
Patient Initials		
Patient Hospital number		
Age		
Gender		
COMORBIDITIES	**Yes**	**No**
1. Hypertension		
2. Diabetes		
3. Cardiac disease		
4. Obesity		
5. Smoking history		
Presenting complaints		
Fever		
Cough		
Dyspnea		
Rhinitis		
Myalgia		
Conjunctivitis		
Headache		
Nausea		
Vomiting		
Diarrhea		

Modified RALE Score	**Right lung**	**Left lung**	**Total Score**
1 – less than 25% lung involvement **2 – 25% to 50% lung involvement** **3 – 50% to 75% lung involvement** **4 more than 75% lung involvement**			

CLINICAL OUTCOME
In- hospital mortality
Discharged

Appendix B: Budget

ITEM	QUANTITY	COST PER UNIT	TOTAL COST
A4 Printing Paper	3 reams	1000	3000
Pens	1 box	1000	1000
Document Folders	10	200	2000
Ethic board Fees	-		2000
Printing	-		3000
Statistician Services	-		30000
Digital Transfer of Images	-		3000
Printing and Binding (draft, proposal, final report)	-		25000
Total			**69000**

Appendix C: Time Plan

	Dec 2020	Jan 2021	April 2021	May 2021	May-Sept 2021	Sept-Oct 2021	Oct 2021
Proposal write up	“						
Correction of supervisor’s input		“					
1st submission to KNH-ERC		“					
2nd submission & corrections			“				
Final submission & expected approval				“			
Data collection					“		
Data entry					“		
Data analysis						“	
Report writing						“	
Dissertation submission							“

Appendix D: KNH/UON-ERC Letter of Approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

9th August , 2021

Ref: KNH-ERC/A/284

KENYATTA NATIONAL HOSPITAL APPROVED 09 AUG 2021 KNH/UoN-ERC P. O. BOX 20723 - 00202 NAIROBI

Dr. Esther C.M. Gumbe
Reg. No.H58/11901/2018
Dept. of Diagnostic Imaging and Rad. Medicine
School of Medicine
College of Medicine
University of Nairobi

Dear Dr. Gumbe

RESEARCH PROPOSAL: CHEST RADIOGRAPHIC SCORES AT ADMISSION CORRELATED TO THE MORTALITY OF COVID-19 PATIENTS AT THE KENYATTA NATIONAL HOSPITAL (P49/02/2021)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 9th August 2021 – 8th August 2022.

This approval is subject to compliance with the following requirements:

i. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
ii. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
iii. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (Attach a comprehensive progress report to support the renewal).
vii. Submission of an executive summary report within 90 days upon completion of the study.

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This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M.L CHINDIA
SECRETARY, KNH- UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chair, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UoN
The Chair, Dept.of Diagnostic Imaging & Radiation Medicine, UoN
Supervisors: Dr. Alfred Odhiambo,Dept.of Diagnostic Imaging and Radiation Medicine, UoN
Dr. Beatrice Mugi, Dept.of Diagnostic Radiology, KNH
Dr.Gladys Mwango, Dept.of Diagnostic Imaging & Radiation Medicine, UoN