ORIGINAL ARTICLE

Risk factors for death including initial admission to COVID-19 quarantine before isolation vs. direct admission to isolation at King Edward VIII hospital in South Africa: A case-control study

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ABSTRACT

Worldwide, the emergence of the novel coronavirus disease 2019 (COVID-19) has resulted in millions of deaths. This study aims to investigate the relationship between death during admission and various risk factors thereof including admission to COVID-19 quarantine before isolation vs. direct admission to isolation, among COVID-19 patients at King Edward VIII Hospital. A case-control study design was employed, involving 400 COVID-19 patients (200 cases and 200 controls by a 1:1 ratio). Patient information was retrospectively abstracted from medical records. Associations between risk factors and mortality were assessed using chi-square tests, followed by univariate and multivariate logistic regression analyses. Among the 200 cases, 133 were referred from primary or secondary levels of care, compared to 71 out of 200 controls. The mean age of patients was 55.6 years (SD: 16.2 years), and 177 (44.2%) patients were male. Out of the total number of patients, 181 (45.2%) patients were initially admitted to the COVID-19 quarantine ward before isolation, while 219 (54.7%) patients were directly admitted to the COVID-19 isolation ward. Increasing age (adjusted odds ratio [aOR]:> 60 years: 6.49 [95%CI: 2.97-14.16]), admission directly to isolation ([aOR]: 2.49[95%CI:1.53-4.06]), Fever ([aOR]: 1.74[95%CI:1.03-2.91]) Shortness of breath ([aOR]: 4.86[95%CI:2.53-9.35]), CKD (Chronic Kidney Disease) ([aOR]: 10.39 [95%CI:2.09-51.61]), and obesity ([aOR]: 4.85[95%CI:1.88-12.46]) were associated with death among COVID-19 patients during admission on multivariate analysis. Understanding and addressing these factors can help healthcare systems develop targeted strategies to improve patient outcomes and reduce mortality rates.

Keywords:
deaths, risk factors, COVID-19, South Africa

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INTRODUCTION

Globally, the novel coronavirus (COVID-19) pandemic has had a significant impact.[1] It has resulted in numerous hospitalizations, particularly in intensive care, and a substantial number of deaths.[2] As of July 6, 2023, there were 691,206,028 confirmed cases and 6,898,266 deaths due to COVID-19 worldwide.[3] Africa was also severely affected by COVID-19, and as of July 6, 2023, South Africa was the most affected country on the continent, with 4,076,463 confirmed cases and 102,595 deaths.[3] COVID-19 is a contagious illness caused by a newly discovered coronavirus, capable of spreading from an infected individual to approximately three other individuals on average within a population.[4] Although most infected people experience only mild symptoms such as shortness of breath, fever, cough, and sore throat, some may develop fatal complications such as respiratory failure, arrhythmia, shock, renal failure, cardiovascular damage, and hepatic failure.[5,11] Global reports have indicated that advanced age, the presence of co-morbidities such as cardiovascular diseases and diabetes, and obesity are linked to more critical outcomes.[6,7] The presence of underlying co-morbidities and limited resources have been identified as contributing factors to the high mortality rate in Africa.[8] We conducted a systematic review and meta-analysis that uncovered significant clinical risk factors associated with mortality outcomes in hospitalized COVID-19 patients in Africa. The study revealed that advanced age (adjusted odds ratio [aOR]: 1.04 [95% CI: 1.02–1.06]), male gender (aOR: 1.23 [95% CI: 1.07–1.40]), hypertension (aOR: 1.56 [95% CI: 1.27–1.85]), diabetes mellitus (aOR: 1.26 [95% CI: 1.01–1.51]), chronic kidney disease (aOR: 3.39 [95% CI: 2.45–4.71]), and severe or critical conditions (aOR: 9.04 [95% CI: 3.14–14.94]) were among the identified factors.[9] Additional risk factors influencing mortality, such as smoking status and elevated D-dimer levels, have been reported to be associated with increased mortality in COVID-19 patients.[16] Despite extensive research, several gaps persist in understanding COVID-19 outcomes. Few studies have investigated the association between quarantine, isolation, and mortality among hospitalized COVID-19 patients, even though these measures are common strategies for managing infectious disease outbreaks and preventing deaths. Additionally, limited research has explored how initial admission to quarantine versus direct isolation impacts patient outcomes, emphasizing the need to determine whether delays in definitive care due to quarantine protocols influence mortality. Furthermore, while global data on risk factors is abundant, there is a notable scarcity of studies focusing on African populations. Region-specific research is crucial to address factors such as genetic predispositions, healthcare infrastructure, and prevalent comorbidities, which may differ from those observed in other regions. Therefore, the present study aims to investigate the relationship between mortality during admission and various associated risk factors, including admission to a COVID-19 quarantine for diagnostic investigation before isolation versus direct admission to COVID-19 isolation after a pre-referral diagnosis, among a subset of COVID-19 diagnosed or suspected patients admitted to King Edward VIII Hospital in Durban, KwaZulu-Natal, South Africa.

METHODS

In South Africa, King Edward VIII Hospital is classified as a tertiary care facility, meaning it provides highly specialized medical services, advanced diagnostics, and treatments not typically available in primary or secondary healthcare facilities. The hospital is equipped with a wide range of medical specialties, including but not limited to obstetrics and gynecology, HIV/AIDS care, pediatrics, surgery, internal medicine, and emergency care. It is also a training center for students from the University of KwaZulu-Natal, Nelson R. Mandela School of Medicine, and the College of Nursing.

In the healthcare system, King Edward VIII Hospital occupies a crucial position within the referral pathway. Patients typically progress through a hierarchical system when seeking medical care.

Primary Care: Patients initially seek healthcare services at local clinics or general practitioners' offices for basic health concerns.

Secondary Care: If the condition requires more specialized attention, patients may be referred to secondary care facilities, such as district hospitals or specialized clinics.

Tertiary Care (King Edward VIII Hospital): In cases where patients require highly specialized diagnostics, treatments, surgeries, or expertise, they are referred to tertiary care institutions like King Edward VIII Hospital. These institutions have specialized medical teams, advanced technology, and a broader range of medical services.

Access to King Edward VIII Hospital typically involves a referral from a primary or secondary healthcare provider, based on the complexity of the medical condition. Once referred, patients may need to go through an appointment scheduling process, which can vary depending on the urgency of the case. Additionally, individuals seeking immediate medical care may present themselves at the hospital's emergency department. This route ensures that patients receive timely medical attention, regardless of the nature of their medical condition.

To effectively manage COVID-19 patients, King Edward VIII Hospital set up dedicated wards for quarantine and isolation:

Quarantine Wards (Person Under Investigation [PUI] Wards): The hospital's quarantine wards, known as "Person Under Investigation" (PUI) wards, were designated for patients exhibiting symptoms of COVID-19 or those who had a history of potential exposure. Patients admitted to these wards underwent thorough diagnostic assessments to determine if they had the virus infection.

Isolation Wards: Once patients tested positive for COVID-19, they were transferred to the hospital's isolation wards. These wards were designed to prevent the spread of the virus by strictly isolating infected individuals from the general patient population.

A case-control study was conducted at King Edward VIII Hospital.

Study Population

Medical records of patients with COVID-19 admitted to the quarantine or isolation wards at King Edward VIII Hospital from March 2020 to December 2021 were reviewed. Cases and controls were selected in a 1:1 ratio, with a total of 400 patients included (200 cases (deaths) and 200 controls (recovered)). Both cases and controls were randomly selected from hospital records.

Inclusion and Exclusion Criteria:

Inclusion Criteria

Case: Patients with COVID-19 (SARS-CoV-2 infection confirmed by polymerase chain reaction [PCR]) who were admitted to the quarantine or isolation ward at King Edward VIII Hospital from March 2020 to December 2021 and whose treatment outcome was death.

Control: Patients with COVID-19 (SARS-CoV-2 infection confirmed by PCR) who were admitted to the quarantine or isolation ward at King Edward VIII Hospital from

March 2020 to December 2021 and recovered from the disease and were discharged alive.

Exclusion Criteria

Patients with COVID-19 whose outcome status was unknown due to transfer to other hospitals or any other reason that resulted in discharge before the outcome could be observed were excluded.

Data Abstraction

All relevant information for cases and controls was gathered retrospectively from patient medical records. Data were extracted using a standardized data extraction form. In addition to quarantine and isolation, information on age, sex, pre-existing co-morbidities (e.g., hypertension, diabetes mellitus, chronic kidney disease (CKD), HIV, any malignancy, chronic respiratory disease, tuberculosis, and obesity, as well as tobacco smoking), symptoms (fever, sore throat, cough, shortness of breath), clinical parameters (pulse, respiratory rate, oxygen saturation on room air), and length of stay were also extracted.

Data Analyses

Data were imported into Stata version 17 from an Excel sheet for analysis. Various study characteristics were presented as proportions or means and compared between cases and controls. To assess the association between different risk factors/variables and death among COVID-19 patients admitted to King Edward VIII Hospital, simple analyses with Chi-square tests were followed by univariate and multivariate logistic regression analyses. The multivariate logistic regression was adjusted for variables that showed a statistically significant ($P < 0.05$) association with death in bivariate analyses, including Chi-square tests and univariate logistic regression analyses. Confounding was adjusted for using multivariate logistic regression, considering age, direct admission to isolation, fever, shortness of breath, and pre-existing co-morbidities (hypertension, diabetes, CKD, and obesity).

Ethical Approval

This study is part of a larger study approved by the University of KwaZulu-Natal/Biomedical Research Ethics Committee (UKZN/BREC) under reference number BREC/00005034/2022.

RESULTS

A total of 400 patients were included in the study: 200 were cases, and 200 were controls. Of the 200 cases, 133 came from the primary and secondary levels of care, while 71 of the 200 controls were from these levels of care. Among the cases, the majority, 63 (31.5%), were from the district hospital, while among the controls, the majority, 106 (53.0%), were from home (Table 1.1). Most of the deceased patients originated from lower levels of care. The mean age of the patients was 55.6 years (SD: 16.2 years), and 44.2% were male (Table 1.2). Of the total number of patients, 181 (45.2%) were initially admitted to the COVID-19 quarantine ward before being transferred to isolation, while 219 (54.7%) were directly admitted to the COVID-19 isolation ward. Among all the admitted patients, 75 (37.5%) died in the quarantine ward, 125 (62.5%) died in the isolation ward, 106 (53.0%) patients were discharged alive from the quarantine ward, and 94 (47.0%) were discharged alive from the isolation ward (Table 1.3).

Regarding the symptoms of COVID-19 at admission, the majority of patients had shortness of breath (317 [79.2%]), followed by cough (270 [67.5%]), fever (125 [31.2%]), and sore throat (97 [24.2%]) (Table 1.3). A history of pre-existing comorbidities was reported in 302 (75.5%) patients. Among them, 175 (43.7%) had hypertension, 131 (32.7%) had diabetes, 102 (25.5%) had HIV, 35 (8.7%) had obesity, 18 (4.5%) had CKD, 12 (3.0%) had current tuberculosis, 22 (5.5%) had a previous history of tuberculosis, 10 (2.5%) had asthma, and 10 (2.5%) had cancer (Table 1.5). "HIV 'yes' indicates a positive HIV status, 'no' refers to a negative status, and 'unknown' refers to an undetermined HIV status."

Regarding the vital signs of COVID-19 patients, 26 (6.5%) had a temperature >38°C, 271 (67.7%) had a respiratory rate >20 breaths/min, 206 (51.5%) had a heart rate >100 beats/min, and 158 (39.5%) had an SpO2 <85% on room air (Table 1.4).

Table 1 (Tables 1.1. - 1.5). Comparisons of the distribution of potential predictors and Chi-square tests of association of predictors with the outcome of interest (death/cases vs. surviving/controls)

Table 1.1 Origin of the patients

Level of care	Origin of the patients	Control Number (%)	Case Number (%)	Total Number (%)	P value
					0.000
Primary level of care	Home	106(53.0)	48(24.0)	154(38.5)	
	Private medical practice	28(14.0)	35(17.5)	63(15.7)	
	Community Health Centre	1(0.5)	3(1.5)	4(1.0)	
	Clinic	3(1.5)	9(4.5)	12(3.0)	
Secondary level of care	Private hospital	8(4.0)	23(11.5)	31(7.7)	
	District hospital	31(15.5)	63(31.5)	94(23.5)	
Tertiary level of care	Regional hospital	10(5.0)	7(3.5)	17(4.2)	
Quaternary level of care	Central hospital	3(1.5)	1(0.5)	4(1.0)	
	Not reported	10(5.0)	11(5.5)	21(5.2)	

Table 1.2 Demographic Characteristics

Variables	Control Number (%)	Case Number (%)	Total Number (%)	P value
Mean (SD) age	50.4(15.1)	60.9(15.5)	55.6(16.2)	
Age group				**0.000**
19-40	55(27.5)	21(10.5)	76(19.0)	
41-60	96(48.0)	75(37.5)	171(42.7)	
> 60	49(24.5)	104(52.0)	153(38.2)	
Sex				**0.920**
Male	88(44.0)	89(44.5)	177(44.2)	
Female	112(56.0)	111(55.5)	223(55.7)	

Table 1.3 Admission to quarantine or isolation and symptoms of COVID-19.

Variables	Control Number (%)	Case Number (%)	Total Number (%)	P value
Admission				**0.002**
Initial admission to COVID-19 quarantine before isolation	106(53.0)	75(37.5)	181(45.2)	
Admission directly to isolation	94(47.0)	125(62.5)	219(54.7)	
Total	200(100.0)	200(100.0)	400(100.0)	
Symptoms				
Fever				**0.013**
Yes	51(25.5)	74(37.0)	125(31.2)	
No	149(74.5)	126(63.0)	275(68.7)	
Cough				**0.393**
Yes	139(69.5)	131(65.5)	270(67.5)	
No	61(30.5)	69(34.5)	130(32.5)	
Sore throat				**0.080**
Yes	56(28.0)	41(20.5)	97(24.2)	
No	144(72.0)	159(79.5)	303(75.7)	
Shortness of breath				**0.000**
Yes	134(67.0)	183(91.5)	317(79.2)	
No	66(33.0)	17(8.5)	83(20.7)	

Table 1.4 Vital signs of COVID-19 patients

Variables	Control Number (%)	Case Number (%)	Total Number (%)	P value
Temperature (°C)				**0.507**
<37	147(73.5)	153(76.5)	300(75.0)	
37-38	37(18.5)	35(17.5)	72(18.0)	
>38	14(7.0)	12(6.0)	26(6.5)	
Missing	2(1.0)	-------	2(0.5)	
Respiratory rate (RR/min)				**0.000**
12-20	86(43.0)	43(21.5)	129(32.2)	
>20	114(57.0)	157(78.5)	271(67.7)	
Heart rate (Beats/min)				**0.000**
60-100	115(57.5)	79(39.5)	194(48.5)	
>100	85(42.5)	121(60.5)	206(51.5)	
Spo2 (%) on RA				**0.000**
95–100	78(39.0)	18(9.0)	96(24.0)	
91–94	52(26.0)	18(9.0)	70(17.5)	
86–90	39(19.5)	36(18.0)	75(18.7)	

<85	30(15.0)	128(64.0)	158(39.5)	
Missing	1(0.5)	-----	1(0.2)	

Abbreviations: RA: room air, SpO2: oxygen saturation

Table 1.5: Pre-existing comorbidity of COVID-19 patients

Variables	Control Number (%)	Case Number (%)	Total Number (%)	P value
Comorbidity				**0.000**
Yes	136(68.0)	166(83.0)	302(75.5)	
No	64(32.0)	34(17.0)	98(24.5)	
Hypertension				**0.000**
Yes	70(35.0)	105(52.5)	175(43.7)	
No	130(65.0)	95(47.5)	225(56.2)	
Diabetes				**0.002**
Yes	51(25.5)	80(40.0)	131(32.7)	
No	149(74.5)	120(60.0)	269(67.2)	
CKD				**0.001**
Yes	2(1.0)	16(8.0)	18(4.5)	
No	198(99.0)	184(92.0)	382(95.5)	
HIV				**0.137**
Yes	58(29.0)	45(22.5)	103(25.7)	
No	142(71.0)	155(77.5)	297(74.2)	
HIV				**0.032**
HIV-negative	68(34.0)	55(27.5)	123(30.7)	
HIV-positive	58(29.0)	45(22.5)	103(25.5)	
HIV-unknown	74(37.0)	100(50.0)	174(43.5)	
Asthma				**0.055**
Yes	8(4.0)	2(1.0)	10(2.5)	
No	192(96.0)	198(99.0)	390(97.5)	
Tuberculosis current				**0.241**
Yes	8(4.0)	4(2.0)	12(3.0)	
No	192(96.0)	196(98.0)	388(97.0)	
Tuberculosis previous				**0.380**
Yes	9(4.5)	13(6.5)	22(5.5)	
No	191(95.5)	187(93.5)	378(94.5)	
Obesity				**0.000**
Yes	7(3.5)	28(14.0)	35(8.7)	
No	193(96.5)	172(86.0)	365(91.2)	
Cancer				**0.055**
Yes	2(1.0)	8(4.0)	10(2.5)	
No	198(99.0)	192(96.0)	390(97.5)	

The simple analyses using Chi-square tests found significant associations between our outcome of interest (cases/deaths vs. controls/survivors) and several variables: level of care or origin of the patients (p=0.000), age (p=0.000), initial admission to COVID-19 quarantine before isolation vs. admission directly to isolation (p=0.002), fever (p=0.013), shortness of breath (p=0.000), hypertension (p=0.000), HIV status (p=0.032), diabetes (p=0.002), CKD (p=0.001), obesity (p=0.000), respiratory rate (RR) (p=0.000), heart rate (p=0.000), and SpO2 on room air (RA) (p=0.000) (Tables 1.1–1.5).

In multivariate analyses, the following variables were associated with death among COVID-19 patients admitted to King Edward VIII Hospital: increasing age (adjusted odds ratio [aOR] > 60 years: 6.49 [95% CI: 2.97–14.16]), direct admission to isolation ([aOR]: 2.49 [95% CI: 1.53–4.06]), shortness of breath ([aOR]: 4.86 [95% CI: 2.53–9.35]), CKD ([aOR]: 10.39 [95% CI: 2.09–51.61]), and obesity ([aOR]: 4.85 [95% CI: 1.88–12.46]) (Table 2). Before adjusting for variables, fever ([aOR]: 1.71 [95% CI: 1.11–2.63]), hypertension ([aOR]: 2.05 [95% CI: 1.37–3.06]), and diabetes ([aOR]: 1.94 [95% CI: 1.27–2.98]) were associated with death due to COVID-19 at King Edward VIII Hospital (Table 2). Among the patients admitted directly to isolation, 101 (46.1%) had an SpO2 level of <85% (Table 3).

Table 2. Association between demographic characteristics, symptoms at admission, quarantine, isolation, pre-existing comorbidity, and deaths of COVID-19 patients at King Edward VIII Hospital.

Variables	Unadjusted OR (95% CI of OR)	P-value	Adjusted OR (95% CI of OR)	P-value
Age group (years)				
19-40	Ref	------	------	------
41-60	2.04(1.13-3.67)	0.017	1.60(0.79-3.22)	0.183
> 60	5.55(3.03-10.19)	0.000	6.49(2.97-14.16)	0.000
Sex				
Female	Ref	------	------	------
Male	1.02(0.68-1.51)	0.920	------	------
Admission				
Initial admission to COVID-19 quarantine before isolation	Ref	------	------	------
Admission directly to isolation	1.87(1.26-2.80)	0.002	2.49(1.53-4.06)	0.000
Symptoms at admission				
Fever	1.71(1.11-2.63)	0.014	1.74(1.03-2.91)	0.035
Cough	0.83(0.54-1.26)	0.393	------	------
Shortness of breath	5.30(2.97-9.44)	0.000	4.86(2.53-9.35)	0.000
Sore throat	0.66(0.41-1.05)	0.081	------	------
Pre-existing comorbidity				
Hypertension	2.05(1.37-3.06)	0.000	1.11(0.65-1.90)	0.682
Diabetes	1.94(1.27-2.98)	0.002	1.62(0.95-2.78)	0.074
CKD	8.60(1.95-37.95)	0.004	10.39(2.09-51.61)	0.004
HIV-negative	Ref			
HIV-positive	0.95(0.56-1.62)	0.877	1.62(0.84-3.12)	0.146

Variables	Unadjusted OR (95% CI of OR)	P-value	Adjusted OR (95% CI of OR)	P-value
HIV-unknown	1.67(1.04-2.66)	0.031	1.71(0.98-2.98)	0.059
Asthma	0.24(0.05-1.15)	0.075	------	------
Tuberculosis current	0.48(0.14-1.65)	0.250	------	------
Obesity	4.48(1.91-10.53)	0.001	4.85(1.88-12.46)	0.001
Cancer	4.12(0.86-19.67)	0.075	------	------

Abbreviations: aOR: adjusted odds ratio, CI: confidence interval, CKD: chronic kidney disease, HIV: human immunodeficiency virus, OR: odds ratio.

Table 3. Oxygen saturation of patients initially admitted to COVID-19 quarantine before isolation vs. patients admitted directly to isolation.

Variable	Patients initially admitted to COVID-19 quarantine before isolation. Number (%)	Patients admitted directly to isolation. Number (%)	P value
SpO2 (%) on RA			**0.039**
95–100	48(26.5)	48(21.9)	
91–94	37(20.4)	33(15.0)	
86–90	39(21.5)	36(16.4)	
<85	57(31.4)	101(46.1)	
Missing	-----	1(0.4)	
Total	181	219	400

Abbreviations: RA: room air, SpO2: oxygen saturation

DISCUSSION

The overall aim of this study was to investigate the relationship between death during admission and various risk factors, including admission to COVID-19 quarantine for diagnostic investigation before isolation versus direct admission to COVID-19 isolation after pre-referral diagnosis, among a subset of COVID-19 diagnosed/suspected patients admitted to King Edward VIII Hospital in Durban, KwaZulu-Natal, South Africa. This study demonstrated that patient death from COVID-19 was associated with increasing age, direct admission to isolation, shortness of breath, chronic kidney disease (CKD), and obesity.

Our results showed that patients admitted directly to COVID-19 isolation after pre-referral diagnosis, among a subset of COVID-19 diagnosed/suspected patients, were associated with death. Patients with COVID-19 who were admitted directly to COVID-19 isolation were twice as likely to die compared to those who were initially admitted to quarantine before isolation. This finding contrasts with another case-control study conducted in India.[58] This may be because patients with severe conditions, who were referred from lower levels of care after their therapy failed to improve their condition, made up the majority of the patients who were admitted directly to isolation at King Edward VIII Hospital. We recommend that specialized medical professionals and advanced equipment be made available at lower levels of care to help decrease the mortality rates of COVID-19 patients. Two previous meta-analyses found that severe or critical conditions were predictors of death in COVID-19 patients.[9, 59]

Our study also found increasing age to be a risk factor associated with death in COVID-19 patients. This finding is consistent with findings from several other studies.[9, 12, 13, 14] The possible reason for this could be that as age increases, various biological changes occur in the immune system, leading to age-related ailments and increased vulnerability to infectious diseases. These changes not only influence the likelihood of getting infected but also impact the progression of diseases and subsequent clinical outcomes.[15] T cells (CD4+, CD8+) and B cells, which are immune cells, experience functional alterations with aging.[16] The immune system remodeling process known as immunosenescence and the risk of immunopathology in aged patients with reduced B and T lymphocyte functions are thought to be the main contributors to older patients' vulnerability to severe COVID-19 disease and death.[17,18] Age-related alterations in innate and adaptive immunity are associated with impaired type-1 interferon (IFN) response. Some SARS-CoV-2 non-structural proteins suppress the type-1 IFN response, which inhibits CD8+ T-cell response to viral infection.[19] Aged patients may be more vulnerable to COVID-19 because of age-related declines in de novo T-cell response and/or the effects of underlying diseases, particularly chronic viral infections like cytomegalovirus (CMV).[18] Older COVID-19 convalescent plasma donors were found to have higher titers of SARS-CoV-2-specific IgG and neutralizing antibodies than younger donors, although the exact origin of the problem is still unknown.[18,20,21] Inflammaging, chronic low-grade inflammatory phenotype (CLIP), persistent viral infections like CMV, and other potential factors like smoking, decreased sex steroid secretion, and accumulated adipose tissue, create an unbalanced pro-inflammatory environment in elderly adults that amplifies additional inflammatory responses in response to SARS-CoV-2 infection and intensifies the cytokine storm. It also affects both viral entry and ACE-2 expression.[18,22] Furthermore, increased type 2 cytokine production results in a reduced ability to stop viral replication and prolongs pro-inflammatory reactions, which can lead to death. Moreover, due to high levels of angiotensin-converting enzyme genes in the heart and lungs, this group may be at an increased risk of death.[23,24,25,26]

Shortness of breath was found to be a risk factor for death in COVID-19 patients in our study, consistent with previous studies.[27,28,29] Therefore, pulmonary embolism and coagulopathy seem to be more common in patients with fever and signs of shortness of breath. This aligns with the higher occurrence of pulmonary embolism among COVID-19 patients observed in Europe.[30] Alternatively, when immunity is compromised for various reasons, the immune system becomes unable to respond in its usual manner to dangers such as fever. This situation makes the person more vulnerable to severe infections, while shortness of breath indicates reduced lung function and is recognized as a symptom of a critical, potentially lethal condition. Patients who consistently experience shortness of breath may have reduced lung capacity, whether due to functional or anatomical reasons. This condition renders them susceptible to viruses such as COVID-19 and unable to effectively handle the resulting strain, often leading to a poor prognosis.[31]

In our study, CKD was reported as a risk factor for death in COVID-19 patients. This was in line with two previous meta-analyses, [32, 33] but contrasted with two other previous meta-analyses.[34, 35] The underlying reason behind this could be that patients with CKD exhibit elevated levels of pro-inflammatory cytokines. The resultant elevation in oxidative stress triggers an inflammatory immune reaction. Patients with compromised immune systems are more susceptible to an increased prevalence of viruses and bacteria that lead to lung infections.[36, 37] The presence of immune system dysfunction and a high prevalence of underlying comorbidities such as hypertension, cardiovascular disease (CVD), and diabetes in patients with CKD partially accounts for this phenomenon.[48] Inflammatory status and compromised immune systems have been linked to chronic kidney disease (CKD).[49] Furthermore, the increased presence of ACE2 receptors in the tubular cells of individuals with CKD can potentially account for the heightened severity of COVID-19 and the poorer prognosis observed in these patients.[50, 51]

Obesity was also identified as an independent risk factor for death in our study. Other studies have similarly reported that obesity contributes to the severity and mortality of COVID-19 patients.[38,39,40] This may be because obesity-related mechanisms are associated with particular fat-resident regulatory T cells and the promotion of TH17 (T cell sub-lineage) biased immunity, both of which are linked to higher prevalence and mortality of COVID-19.[41,42,43] Certainly, these processes are influenced by elevated levels of IL-6, as well as IL-23/IL-17, TNF-α, transforming growth factor (TGF), pro-inflammatory cytokine macrophage migration inhibitory factor, and macrophage inflammatory protein 1α.[44] Furthermore, poor ventilatory lung mechanics associated with obesity and an increased risk for pro-inflammatory and prothrombotic states are potential poor prognostic variables in severe illnesses like the H1N1 flu and probably have an impact on COVID-19 outcomes.[45, 46, 47] Obesity involves more than just the accumulation of fat under the skin. It also encompasses the accumulation of excess fat in various non-typical locations, such as around the organs (visceral adipose tissue), surrounding blood vessels (perivascular adipose tissue), and on the outer surface of the heart (epicardial adipose tissue). Numerous research studies have demonstrated that the distribution of fat contributes to chronic pro-inflammatory, prothrombotic, and vasoconstrictive states, which can manifest as insulin resistance, type 2 diabetes, hypertension, atherosclerosis, cardiovascular disease, and weakened immune function.[52–56] In addition to chronic disease, the presence of visceral adiposity also contributes to heightened mortality rates in critically ill patients suffering from acute respiratory distress syndrome.[57]

In conclusion, addressing risk factors at their source is crucial to improving outcomes for COVID-19. Ensuring the availability of specialized healthcare professionals and advanced equipment at primary and secondary levels of care can significantly reduce the mortality rates of COVID-19 patients admitted directly to isolation at King Edward VIII Hospital. Many patients are referred or admitted in the advanced stages of the disease, limiting the effectiveness of interventions despite direct admission to the isolation ward. Efforts to improve patient outcomes should begin at the primary healthcare level, where patients presenting with symptoms or testing positive can be placed in quarantine for initial observation. This would allow early assessment of risk factors and disease severity before patients require isolation. Alternatively, bypassing primary and secondary healthcare for patients with severe symptoms and directing them to tertiary hospitals may prevent delays in specialized treatment and improve survival chances.

RECOMMENDATION

Here are some recommendations based on the results of the study:

Optimizing Triage and Admission Pathways: Strengthening triage protocols at primary and secondary levels, can help identify high-risk patients earlier and prevent delays in critical care. We recommend equipping lower-level facilities with specialized medical personnel and advanced equipment to improve patient outcomes. Additionally, we recommend not strictly adhering to the hierarchical health system process during the outbreak.

Enhanced Management of Comorbidities: Healthcare systems should enhance early screening and management of these conditions, particularly in patients at risk of severe COVID-19 outcomes. The healthcare system should implement community-based prevention programs: Given the high prevalence of conditions such as obesity, hypertension, HIV, and diabetes, there is a critical need for community-level health promotion efforts.

Enhanced Focus on Early Symptom Management: Patients presenting with respiratory distress should receive oxygen supplementation promptly, and healthcare providers should be trained to recognize early signs of respiratory failure. Aggressive fever management, including antipyretics and proper hydration, should be a priority in the early stages of infection.

Age-Specific Strategies: Tailored care protocols should be developed to ensure that older patients receive timely and intensive interventions, including early mechanical ventilation or other supportive measures when needed.

AUTHOR CONTRIBUTIONS

R.G.M.: Conceptualization, Methodology, Data collection, Data Curation, Formal Analysis, Writing – Original Draft. T.W.M.: Data Collection, Resources, Validation, Writing – Review & Editing. F.B.E.: Data Collection, Software, Writing – Review & Editing. W.H.C.: Formal Analysis, Visualization, Writing – Review & Editing. B.M.: Investigation, Data Curation, Writing – Review & Editing. N.M.: Conceptualization, Supervision, Writing – Review & Editing.

ETHICAL CONSIDERATION

The ethics committee that approved this study is the University of KwaZulu-Natal Biomedical Research Ethics Committee (UKZN/BREC). The approval/ protocol number is BREC/00005034/2022, and the date of approval is 03 April 2023.

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