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Epidemiology of laboratory-confirmed SARS-CoV-2 hospitalized cases in a tertiary hospital, Gauteng Province, South Africa, 1 April 2020 to 31 March 2021

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EPIDEMIOLOGY OF LABORATORY-CONFIRMED SARS-COV-2 HOSPITALIZED CASES IN A TERTIARY HOSPITAL, GAUTENG PROVINCE, SOUTH AFRICA, 1 APRIL 2020 TO 31 MARCH 2021

Mpho Lerato Sikhosana

A Research Report submitted to the Faculty of Science, University of the Witwatersrand, in fulfilment of the requirements for the degree of Master of Medicine in Virology.

Johannesburg, 2021.

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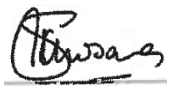
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1. DECLARATION

I, **Mpho Lerato Sikhosana**, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of **Master of Medicine in Virology** at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



2nd day of December 2021 in Brakpan

2. ABSTRACT

Epidemiology of laboratory-confirmed SARS-CoV-2 hospitalized cases in a tertiary hospital, Gauteng Province, South Africa, 1 April 2020 to 31 March 2021

Gauteng Province (GP) was the most affected province in South Africa during the first year of the COVID-19 pandemic. We aimed to describe the epidemiology of COVID-19 cases admitted in one of the largest quaternary hospitals in the province during the two pandemic waves. We used data from the national hospital surveillance system, DATCOV, that recorded COVID-19 admissions at Charlotte Maxeke Johannesburg Academic Hospital in (GP) from 5 March 2020 to 27 March 2021. We used multivariable logistic regression to determine a) factors associated with hospitalization in the second compared to the first pandemic wave, and b) factors associated with in-hospital mortality. There were 1861 cases admitted during the study period. The mean age of the cases was 50 (IQR 37-61), 51.80% were females, and 58.68% were black. Of the total number of admissions, 2.10% were healthcare worker, 53.85% of whom were nurses. On admission, 91.99% of cases were admitted at a general ward while 5.86% were admitted at an intensive care unit. Overall, 10.59% of the cases required intensive care during their hospital stay. The case fatality ratio was the highest (28.54%) during wave 2 and lowest during pre-wave 1 (11.49%). Compared to the first wave, factors associated with hospitalization during the second wave included age ≥80 years (adjusted odds ratio [aOR] 3.43, 95% CI 1.07-10.98) compared to ages 0-19 years, as well as being of other race (aOR 5.63, 95%CI 1.84-17.20) compared with White race. Regarding in-hospital mortality, associated factors included age groups 60-79 (aOR 4.53, 95%CI 1.03-19.86) and ≥80 (aOR 9.63, 95%CI 1.93-48.01) compared to ages 0-19 years; male sex (aOR 1.55, 95%CI 1.16-2.08); presence of an underlying comorbidity (aOR 1.99, 95%CI 1.45-2.71) as well as being admitted during the second wave (aOR 1.54, 95%CI 1.12-2.10). Our study found that there was a higher risk of mortality during the second compared to the first wave, and other factors associated with mortality included older age, being male as well as having an existing comorbidity. These findings will help inform prevention strategies required to prevent high mortality rates during future waves of infection.

Word count: 334

Keywords: COVID-19, hospitalization, in-hospital mortality, comorbidities

3. ACKNOWLEDGEMENTS

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5. NOMENCLATURE

a. ACE2 α: angiotensin converting enzyme 2 aplha
b. aOR: adjusted odds ratio
c. cART: combination antiretroviral therapy
d. CFR: Case Fatality Ratio
e. CMJAH: Charlotte Maxeke Johannesburg Academic Hospital
f. DATCOV: South African national hospital surveillance system
g. GP: Gauteng Province
h. HCW: Healthcare workers
i. ICU: intensive care unit
j. IQR: interquartile range
k. LOS: Length of hospital stay
l. NPIs: Non-pharmaceutical interventions
m. SARS-CoV-2: SARS Coronavirus 2
n. TB: tuberculosis
o. TMPRSS2: transmembrane protease serine 2
p. uOR: unadjusted odds ratio

6. CHAPTER ONE – INTRODUCTION

General Introduction

The initial cases of COVID-19 in South Africa were imported, with most of the individuals having travelled to Europe (1). The cases were distributed in three of the country's provinces, namely Gauteng, Kwa-Zulu Natal and Western Cape, wherein most international travels occurred and most of the country's urban populations resided (2). When local transmission was established in the country, the rise in SARS-CoV-2 test requests resulted in a burden on the country's laboratory testing capacity and subsequent prolonged turnaround time of results. This led to the revision of the country's testing strategy, prioritizing the testing of hospitalized patients, symptomatic Healthcare Workers (HCW) and their close contacts, as well as high-risk cohort groups such as in long-term care facilities (3).

According to DATCOV, a South African sentinel hospital surveillance system reporting on the epidemiological and clinical characteristics as well as outcomes of COVID-19 hospitalised patients in both public and private hospitals in the country, factors associated with severe COVID-19 and mortality included older age groups above 50 years, the male sex as well as comorbidities such as hypertension, diabetes, chronic cardiac disease and chronic lung disease (4). Based on provincial deaths data from 28 March to 3 July 2020, the median age of death amongst fatalities was 61 years, with mortality being 1.5 times higher in males compared to females and amongst affected individuals with comorbidities including hypertension and diabetes.

By the end of the first year of the pandemic, 1 517 666 laboratory confirmed cases and 50 462 deaths had been reported and two waves of infections had occurred (first wave reported from 7 June - 22 August 2020 and the second wave from 15 November 2020 - 6 February 2021) (5,6). Gauteng Province (GP) was the most affected province during the first year of the pandemic, with 405 860 cases (26.7%) and 9 797 (19.4%) deaths reported (5). Of the province's five districts, the Johannesburg District was the province's COVID-19 epicentre (7). Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), an academic quaternary hospital in GP located in the Johannesburg District,

was one of three healthcare facilities initially designated to manage COVID-19 cases in GP at the beginning of the pandemic.

Objectives

The study objectives included:

1.2.1 To describe and compare the characteristics of hospitalized COVID-19 patients during the first and second waves were compared in GP

1.2.2 To determine factors associated with in-hospital mortality

7. CHAPTER TWO – METHODS AND MATERIALS

This cross-sectional study used secondary analysis of data from the South African national hospital surveillance system, DATCOV, that captured data on COVID-19 hospital admissions since 5 March 2020 till 27 March 2021. The data analysed were of patients admitted at CMJAH, a 1088-bed hospital with intensive and high-care facilities offering tertiary, secondary and highly specialized services, and that is located in the City of Johannesburg in GP (8). Data of all patients who were diagnosed with confirmed SARS-CoV-2 infection and subsequently admitted at CMJAH during the study period were included in the study. A hospital admission was defined as a confirmed hospital stay of >1 day regardless of the reason for admission or age. Individuals who were not classified as white, black, coloured, or Indian were reported as “other” and for the purposes of this study, “other” was categorised as a minority group.

In order to compare this study’s findings with national data, we divided the study period into 5 wave periods using the methodology developed by the National Institute for Communicable Diseases, when the country's weekly incidence risk was 5 admissions per 100000 people at the beginning and at the end of the wave period (6). The wave periods were pre-wave 1 (5 March - 6 June 2020), wave 1 (first wave; 7 June - 22 Aug 2020), post-wave 1 (23 Aug - 14 Nov 2020), wave 2 (second wave; 15 Nov 2020 - 6 Feb 2021) and post-wave 2 (7 Feb – 27 March 2021) (6). Case fatality risk per month was calculated by using the number of COVID-19 related deaths for a particular month as the numerator and the sum of COVID-19 deaths and cases discharged alive for the same month as the denominator. Using multivariable logistic regression models, (a) characteristics of hospitalized COVID-19 patients during the first and second waves were compared, and (b) factors associated with in-hospital mortality were assessed. Stata statistical software version 15 was used for data analysis (StataCorp®, College Station, Texas, USA). Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee of the University of the Witwatersrand (Ethics reference number M210716).

8. CHAPTER THREE - RESULTS

There were 1861 SARS-CoV-2 cases admitted at CMJAH from 5 March 2020 to 27 March 2021 (Table 1), 984 (51.80%) of whom were female. There were more cases amongst the 30-39 (336; 18.05%), 40-49 (360; 19.34%) and 50-59 (412; 22.14%) age groups. The mean age (interquartile range [IQR]) of all admitted cases was 50 years (IQR 37-61). The mean age was the highest in wave 2 (53years; IQR 40-63) and post-wave 2 (53years; IQR 42-63). Majority of the cases were black (1092; 58.68%) while the least cases admitted belonged to the coloured (23; 1.24%) and other (35; 1.88%) races. Of the 1861 admitted cases, only 39 (2.10%) were healthcare workers (HCWs), 21 (53.85%) of whom were nurses, and 2 (5.13%) of whom were doctors. Higher proportions of HCWs were admitted during pre-wave 1 (8; 20.51%) and wave 1 (26; 66.67%).

On admission, 1712 (91.99%) cases were admitted in a general ward and 109 (5.86%) in the intensive care unit (ICU). Regarding the highest level of care during hospital admission, 1629 (87.53%) of cases were treated in the general wards, 197 (10.59%) in ICU and 35 (1.88%) in high care units. Of the 197 cases whose highest level of care was in ICU, a higher proportion of such patients were treated during wave 2 (98; 49.75%) and wave 1 (49; 24.87%). Over two-thirds of the cases (1431; 76.89%) were discharged alive, while 392 (21.06%) died due to COVID-19 complications. The median length of hospital stay (LOS) was 7 days (IQR 4-11), with the LOS being longest during post-wave 1 (8 days; IQR 5-13) and post-wave 2 (8 days; IQR 5-12). The shortest LOS was during wave 1 (6 days; IQR 3-10). Due to the high proportion of missing data, we could not analyse the signs and symptoms that the patients presented with on admission. However, cases were classified according to reasons for admission, including “COVID-19 symptoms” (1367 cases [85.87%]), “isolation” (6 cases [0.38%]), or admission for other reason (219 cases [13.76%]).

Regarding the clinical management of cases, frequently used medications included antibiotics, steroids and anticoagulants (Table 2). There were 857 (32.12%) cases that received antibiotics, the use of which consistently decreased with each wave period. Over seven hundred cases (785, 29.42%) received steroids, with the proportion being roughly similar across each wave period. Two hundred and eighty (10.49%) cases received

anticoagulants, the use of which increased later in the pandemic. There was low use of antivirals and immunotherapies, however colchicine continued to be used in every wave period, with a total of 497 (18.63%) cases having been treated with this drug.

The monthly case fatality ratio (CFR) peaked at 18.98% in July 2020 during the first wave, while the peak monthly CFR in the second wave was 23.45% in December 2020 (Table 3). The most COVID-19 associated deaths occurred in wave 1 (190) and wave 2 (147), with the mortality rates of 20.34% and 28.54% respectively (Table 4).

The most prevalent comorbidities amongst the cases were hypertension (567; 30.47%), diabetes (402; 21.60%) and HIV (204; 10.96%) (Table 5). There were 36 (1.93%) cases admitted with active tuberculosis (TB) while 24 cases (1.29%) had a history of previous TB infection (Table 4). Of the 204 cases with HIV, information on combination antiretroviral (cART) use was available for 171 cases, of which 143 (83.63%) were on cART and 28 (16.37%) were treatment naïve.

Factors associated with being hospitalized in the second wave compared to the first wave were age $\geq$80 years (adjusted odds ratio [aOR] 3.43; 95% confidence interval [95% CI] 1.07-10.98) as well as belonging to the other race (aOR 5.63; 95% CI 1.84-17.20), while factors less common with hospital admission in the second wave was being of Indian descent (aOR 0.32; 95% CI 0.12-0.82) (Table 6).

Factors associated with COVID-19 mortality were age groups 60-79 years (aOR 4.53; 95% CI 1.03-19.86) and $\geq$80 years (aOR 9.63; 95% CI 1.93-48.01) compared to the age group 0-19 years, male sex (aOR 1.55, 1.16-2.08), having a comorbid condition (aOR 1.99, 1.45-2.71) and admission during the second pandemic wave compared to the first wave (aOR 1.54, 1.12 – 2.10). (Table 7).

347 **Table 1.** Characteristics of COVID-19 cases admitted at Charlotte Maxeke Hospital, 05 March 2020 – 27 March 2021

Variable	Pre-wave 1		Wave 1		Post-wave 1		Wave 2		Post-wave 2		Total		p value
	n	%	n	%	n	%	n	%	n	%	n	%	
Age													**<0.001**
0-9	2	1.32	20	2.11	3	2.44	7	1.33	0	0	32	1.72	
10-19	3	1.97	20	2.11	4	3.25	4	0.76	1	0.91	32	1.72	
20-29	18	11.84	81	8.54	17	13.82	35	6.63	8	7.27	159	8.54	
30-39	48	31.58	165	17.41	29	23.58	79	14.96	15	13.64	336	18.05	
40-49	31	20.39	192	20.25	18	14.63	99	18.75	20	18.18	360	19.34	
50-59	23	15.13	210	22.15	18	14.63	130	24.62	31	28.18	412	22.14	
60-69	22	14.47	146	15.40	21	17.07	99	18.75	20	18.18	308	16.55	
70-79	2	1.32	90	9.49	10	8.13	56	10.61	11	10.00	169	9.08	
80+	3	1.97	22	2.32	3	2.44	19	3.60	4	3.64	51	2.74	
Unknown	0	0	2	0.21	0	0	0	0	0	0	2	0.11	
Mean Age in years (interquartile range)	42 (IQR: 32-54)		49 (IQR: 37-60)		44 (IQR: 31-61)		53 (IQR: 40-63)		53 (IQR: 42-63)		50 (IQR 37-61)		
Sex													0.054
Female	65	42.76	488	51.48	54	43.90	289	54.73	68	61.82	984	51.80	
Male	87	57.24	459	48.42	69	56.10	239	45.27	42	38.18	896	48.15	

Table 1. Characteristics of COVID-19 cases admitted at Charlotte Maxeke Hospital, 05 March 2020 – 27 March 2021, continued

Variable	**Pre-wave 1**		**Wave 1**		**Post-wave 1**		**Wave 2**		**Post-wave 2**		**Total**		**p value**
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Race													**<0.001**
Black African	97	63.82	469	49.47	53	43.09	380	71.97	93	84.55	1092	58.68	
White	5	3.29	30	3.16	2	1.63	24	4.55	7	6.36	68	3.65	
Indian	8	5.26	31	3.27	3	2.44	8	1.52	0	0	50	2.69	
Other	0	0	5	0.53	2	1.63	21	3.98	7	6.36	35	1.88	
Coloured	4	2.63	8	0.84	0	0	9	1.70	2	1.82	23	1.24	
Unknown	38	25.00	405	42.72	63	51.22	86	16.29	1	0.91	593	31.86	
Healthworker													**0.002**
No	144	94.74	922	97.26	123	100	524	99.24	109	99.09	1822	97.90	
Yes	8	5.26	26	2.74	0	0	4	0.76	1	0.91	39	2.10	
Healthworker speciality													**0.012**
Nurse	4	50	15	57.69	0	0	1	25.00	1	100	21	53.85	
Doctor	0	0	1	3.85	0	0	1	25.00	0	0	2	5.13	
Allied Health	0	0	2	7.69	0	0	0	0	0	0	2	5.13	
Administrators / porters	0	0	0	0	0	0	2	50.00	0	0	2	5.13	
Other	4	50	8	30.77	0	0	0	0	0	0	12	30.77	

Table 1. Characteristics of COVID-19 cases admitted at Charlotte Maxeke Hospital, 05 March 2020 – 27 March 2021, continued

Variable	Pre-wave 1		Wave 1		Post-wave 1		Wave 2		Post-wave 2		Total		p value
	n	%	n	%	n	%	n	%	n	%	n	%	
Ward at admission													**<0.001**
General ward	134	88.16	907	95.68	114	92.68	457	86.55	100	90.91	1712	91.99	
Intensive Care	16	10.53	21	2.22	8	6.50	55	10.42	9	8.18	109	5.86	
High Care	1	0.66	20	2.11	1	0.81	16	3.03	1	0.91	39	2.10	
Isolation	1	0.66	0	0	0	0	0	0	0	0	1	0.05	
Highest level of care													**<0.001**
General ward	133	87.50	881	92.93	111	90.24	415	78.60	89	80.91	1629	87.53	
Intensive Care	18	11.84	49	5.17	12	9.76	98	18.56	20	18.18	197	10.59	
High Care	1	0.66	18	1.90	0	0	15	2.84	1	0.91	35	1.88	
Length of hospital stay (interquartile range)	7 (3-13)		6 (3-10)		8 (5-13)		7 (4-12)		8 (5-12)		7 (4-11)		
Outcome													**<0.001**
Discharged alive	131	86.18	744	78.48	104	84.55	368	69.70	84	76.36	1431	76.89	
Died (COVID-19)	17	11.18	190	20.04	15	12.20	147	27.84	23	20.91	392	21.06	
Transfer to other facility	3	1.97	7	0.74	0	0	10	1.89	3	2.73	23	1.24	
Died (non-COVID-19)	1	0.66	6	0.63	4	3.25	3	0.57	0	0	14	0.75	
In Hospital	0	0	1	0.11	0	0	0	0	0	0	1	0.05	

348 **Table 2.** Medication used by COVID-19 cases during admission, Charlotte Maxeke Hospital, 05 March 2020 - 27 March 2021

Medication	**Pre wave 1 (n=114)**		**Wave 1 (n=1072)**		**Post wave 1 (n =111)**		**Wave 2 (n=1216)**		**Post wave 2 (n=155)**		**Total (n=2668)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Antibiotics	44	38.60	405	37.78	37	33.33	333	27.38	38	24.52	857	32.12
Steroids	32	28.07	346	32.28	33	29.73	334	27.47	40	25.81	785	29.42
Anticoagulants	6	5.26	0	0	8	7.21	225	18.50	41	26.45	280	10.49
Anti-inflammatories	0	0	51	4.76	9	8.11	16	1.32	4	2.58	80	3.00
Antifungals	1	0.88	33	3.08	6	5.41	14	1.15	3	1.94	57	2.14
Antivirals	5	4.39	30	2.80	1	0.90	3	0.25	0	0	39	1.46
Chloroquine	12	10.53	1	0.09	0	0	0	0	0	0	13	0.49
Immunotherapies												
Colchicine	10	8.77	183	17.07	17	15.32	263	21.63	24	15.48	497	18.63
Tocilizumab	0	0	13	1.21	0	0	24	1.97	5	3.23	42	1.57
Immunosuppresant not specified	1	0,88	7	0.65	0	0	0	0,	0	0	8	0.30
Immunoglobulin not specified	1	0.88	0	0	0	0	2	0,16	0	0	3	0.11
Polygam	1	0.88	0	0	0	0	2	0.16	0	0	3	0.11
Interferon alpha	0	0	1	0.09	0	0	0	0	0	0	1	0.04
Interferon beta	0	0	1	0.09	0	0	0	0	0	0	1	0.04
Mycophenolate mofetil	1	0.88	0	0	0	0	0	0	0	0	1	0.04
Hydroxychloroquine	0	0	1	0.09	0	0	0	0	0	0	1	0.04

Table 3. COVID-19 in-hospital case fatality ratio at Charlotte Maxeke Hospital by month, March 2020 - March 2021

	COVID-19 deaths	Outcomes	CFR (%)
Mar-20	0	3	0.00
Apr-20	3	27	10.00
May-20	5	33	13.16
Jun-20	51	334	13.25
Jul-20	115	491	18.98
Aug-20	33	184	15.21
Sep-20	8	92	8.00
Oct-20	3	18	14.29
Nov-20	5	20	20.00
Dec-20	34	111	23.45
Jan-21	93	310	23.08
Feb-21	33	136	19.53
Mar-21	9	57	13.64

Table 4. COVID-19 in-hospital case fatality ratio by wave period at Charlotte Maxeke Hospital, March 2020 - March 2021

Outcome	Pre-wave 1	Wave 1	Post-wave 1	Wave 2	Post-wave 2	Total
Alive (n)	131	744	104	368	84	1431
Dead (n)	17	190	15	147	23	392
Mortality (%)	11.49	20.34	12.61	28.54	21.50	21.50

370 **Table 5.** Comorbidities reported in COVID-19 cases admitted at Charlotte Maxeke Hospital, 5 March 2020 - 27 March 2021

Comorbidity	**n**	**%**
Hypertension	567	30.47
Diabetes	402	21.60
HIV		
Negative	836	44.92
Positive	204	10.96
Unknown	821	44.11
HIV treatment status (n=189)		
Experienced	143	75.66
Naive	28	14.81
Unknown	18	9.52
HIV virological suppression (n=189)	70	3.76
Yes	51	26.98
Tuberculosis		
Active	36	1.93
Past	24	1.29
Obesity	192	10.32

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373 **Table 6.** Univariate and multivariate analyses of factors associated with admission to hospital in the first and second COVID-19 waves at
374 Charlotte Maxeke Hospital, 5 March 2020 - 27 March 2021

	Wave period				**Univariate**		**Multivariate**	
	Cases in wave 1		**Cases in wave 2**		**OR 95% CI**		**OR 96% CI**	
	n	**%**	**n**	**%**	**OR**	**95% CI**	**OR**	**95% CI**
Age								
0-19	40	4.23	11	2.08	1 (ref)		1 (ref)	-
20-39	246	26	114	21.59	1.69	0.83 – 3.40	1.39	0.56 - 3.45
40-59	402	42.49	229	43.37	**2.07**	**1.04 – 4.12**	1.67	0.68 - 4.08
60-79	236	24.95	155	29.36	**2.39**	**1.19 – 4.80**	1.81	0.73 - 4.48
80+	22	2.33	19	3.60	**3.14**	**1.27 – 7.78**	**3.43**	**1.07 - 10.98**
Sex								
Female	488	51.53	289	54.73	1 (ref)		-	-
Male	459	48.47	239	45.27	0.88	0.71 - 1.09	-	-
Comorbidities								
No	427	45.04	231	43.75	1 (ref)		-	-
Yes	521	54.96	297	56.25	1.05	0.85 - 1.31	**-**	**-**

Table 6. Univariate and multivariate analyses of factors associated with admission to hospital in the first and second COVID-19 waves at Charlotte Maxeke Hospital, 5 March 2020 - 27 March 2021, continued

	Wave period				**Univariate**		**Multivariate**	
	Cases in wave 1		**Cases in wave 2**		**OR 95% CI**		**OR 96% CI**	
	n	**%**	**n**	**%**	**OR**	**95% CI**	**OR**	**95% CI**
Race								
White	30	5.52	24	5.43	1 (ref)		1 (ref)	-
Black	469	86.37	380	85.97	1.01	0.58 - 1.76	1.07	0.61 - 1.87
Coloured	8	1.47	9	2.04	1.41	0.47 - 4.20	1.51	0.50 - 4.51
Indian	31	5.71	8	1.81	0.32	0.13 - 0.83	**0.32**	**0.12 - 0.83**
Other	5	0.92	21	4.75	5.25	1.72 - 15.98	**5.63**	**1.84 - 17.20**

384 **Table 7.** Univariate and multivariate analyses of factors associated with mortality due to COVID-19 at Charlotte Maxeke Hospital, 5 March
385 2020– 27 March 2021

	Outcome				**Univariate**		**Multivariate**	
	Discharged alive		**Died**		**OR 95% CI**		**OR 96% CI**	
	n	**%**	**n**	**%**	**OR**	**95% CI**	**OR**	**95% CI**
Age								
0-19	57	89.06	7	10.94	1 (ref)		1 (ref)	
20-39	437	90.48	46	9.52	0.86	0.37 – 1.99	1.21	0.27 – 5.42
40-59	594	78.36	164	21.64	2.25	1.01 – 5.02	2.51	0.58 – 10.92
60-79	316	67.96	149	32.04	3.84	1.71 – 8.62	**4.53**	**1.03 – 19.86**
80+	26	50.98	25	49.02	7.83	3.00 – 20.41	**9.63**	**1.93 – 48.01**
Sex								
Female	770	81.31	177	18.69	1 (ref)		1 (ref)	
Male	660	75.49	215	24.57	1.42	1.13 – 1.77	**1.55**	**1.16 – 2.08**
Comorbidities								
No	742	85.09	130	14.91	1 (ref)		1 (ref)	
Yes	689	72.45	262	27.55	2.17	1.72 - 2.74	**1.99**	**1.45 – 2.71**

Table 7. Univariate and multivariate analyses of factors associated with mortality due to COVID-19 at Charlotte Maxeke Hospital, 5 March 2020– 27 March 2021, continued

	Outcome				**Univariate**		**Multivariate**	
	Discharged alive		**Died**		**OR 95% CI**		**OR 96% CI**	
	n	**%**	**n**	**%**	**OR**	**95% CI**	**OR**	**95% CI**
Race								
White	43	64.18	24	35.82	1 (ref)		1 (ref)	
Black	831	78.17	232	21.83	0.50	0.30 - 0.84	0.61	0.35 – 1.06
Coloured	19	82.61	4	17.39	0.38	0.11 - 1.24	0.40	0.12 – 1.38
Indian	38	77.55	11	22.45	0.52	0.22 - 1.20	0.56	0.23 – 1.34
Other	30	85.71	5	14.29	0.30	0.10 - 0.87	**0.27**	**0.09 – 0.82**
Wave period								
Wave 1	744	79.66	190	20.34	1 (ref)		1 (ref)	
Pre-wave 1	131	88.51	17	11.49	0.51	0.30 – 0.86	0.57	0.29 – 1.10
Post-wave 1	104	87.39	15	12.61	0.56	0.32 – 0.99	0.68	0.30 – 1.54
Wave 2	368	71.46	147	28.54	1.56	1.22 – 2.01	**1.54**	**1.12 – 2.10**
Post-wave 2	84	78.50	23	21.50	1.07	0.66 – 1.75	1.18	0.70 – 2.02

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9. CHAPTER FOUR- GENERAL DISCUSSION AND CONCLUSION

Discussion

Our study showed that factors associated with COVID-19 hospitalization in the second wave included age ≥80 years and Indian and other race. COVID-19 in-hospital mortality was associated with age ≥ 60 years, male sex, having a comorbidity and admission during wave 2. These findings have been described in our setting (9) as well as in systematic reviews (10-14).

According to our findings, individuals aged +80 years were more likely to be hospitalized in the second wave compared to those aged 0-19 years. Studies have shown that, compared to the first wave, most infections in the second wave occurred amongst younger individuals, and as a result, the length of hospital stay as well as case fatality ratios were lower (15, 16). The shift in the age of the infections has been purported to be due to better shielding of the older most vulnerable groups, poor compliance to non-pharmaceutical interventions (NPIs) especially social distancing by younger age groups, as well as to biological differences of the variants that circulated during the two waves with regards to increased transmissibility (15). A reason for our finding that over 80s were more likely admitted in the second wave, could be older age groups adhering less to the NPIs, and being more susceptible because they were shielded during earlier wave periods and were now infected by the highly transmissible Beta variant. We also found that ages 60-79 and +80 were significantly associated with in-hospitality. This is consistent with findings locally as well as in other settings (6,17, 18). Increasing age is associated with an increase in prevalence of comorbidities and this would explain the increased risk of COVID-19 mortality amongst older patients.

We found that male sex was associated with COVID-19 death amongst admitted cases. Being male has been identified as a risk factor for COVID-19 related adverse clinical outcomes including mortality (9, 19), and may be explained by biological sex-specific differences in immune responses and regulation of ACE2 and TMPRSS2, the receptor and protease primer respectively, as well as gender-based differences in health behaviours (20-

22). The finding of male predominance has also been described in the setting of epidemics associated with two other coronaviruses, that is SARS CoV-1 (2002 - 2003) and MERS (2012 - 2013) (19). This finding has been recognized as being important from the point of view of the need to encourage males to seek medical care earlier, for instituting more aggressive inpatient care for male patients and promoting vaccination in this population group.

Our findings showed that the presence of an underlying comorbid illness was associated with adverse clinical outcomes amongst cases, similar to what has been reported in the literature locally and globally in both adults and children (9, 23, 24). Comorbidities that were commonly recorded amongst hospitalized COVID-19 cases in the South African DATCOV surveillance system included hypertension (37.4%), diabetes (27.4%) and HIV (9.1%), while comorbidities associated with in-hospital mortality included hypertension, diabetes, chronic renal disease, chronic cardiac disease, malignancy during the past 5 years, HIV, as well as past and current tuberculosis infection (9). This is in keeping with the high national background prevalence of these comorbidities (HIV (19%), hypertension (44 - 46%), diabetes (8 - 13%) and obesity (11 - 41%) (25).

The monthly CFR at CMJAH peaked in July 2020 during the first wave, which is similar to the peak reported from national data, while the peak monthly CFR during the second wave was in December 2020, one month earlier compared to the peak of the second wave according to national data in January 2021 (9). Our finding also revealed that mortality during wave 2 was higher compared to mortality during wave 1. This increased in-hospital mortality during wave 2 compared to wave 1 has been associated with higher admission rates of older patients, higher admissions in the public healthcare sector as well as the possible contribution of the more transmissible circulating beta virus variant (6). The high hospital admissions and in-hospital mortality rates amongst the elderly in the second wave emphasizes the importance of prioritizing the vaccination of the vulnerable elderly in order to prevent high mortality rates during future waves of infection, as has been achieved in other settings (26).

Patients were more likely to be admitted in ICU in wave 2 (98 cases, 18.56%). This is consistent with in-hospital mortality being the highest during wave 2, a finding that has also been reported in our setting at a national level (6).

The management of COVID-19 inpatients has evolved ever since the emergence of the disease, and now includes the use of oxygen therapy, steroids, anticoagulants, antipyretics, and the appropriate management of comorbidities (27-30). Medications that were consistently used throughout the study period included antibiotics and steroids. Although the use of steroids was in keeping with published recommendations, we found that most (642/785; 82%) of the patients in whom steroids were used were not ventilated. By the beginning of the second wave, steroids were included in clinical guidelines, with their benefit in reducing mortality reported particularly in COVID-19 patients requiring oxygen (28, 31). Specifically, guidelines highlighted the lack of benefit of using steroids in patients in whom oxygen support was not required. Similarly, the continued use of antibiotics throughout the study period was not in keeping with recommendations. Withholding antibiotics in patients in whom COVID-19 infection had been confirmed, as well as withdrawing antibiotics if the latter were used empirically in the initial management of the patient had also been included in guidelines by the beginning of the second wave (28). This was on account of bacterial co-infections in COVID-19 cases having been found to be uncommon in our and other settings and the findings not supporting the use of empiric antibiotics in COVID-19 patients (30, 32-34). The high use of antibiotics despite the rare bacterial co-infections and the need to strengthen antimicrobial stewardship has been reported (30, 32-34). Evidence of the occurrence of thrombotic events amongst COVID-19 patients was available as early as April 2020 (35-38). By the end of the first wave, there had been significant evidence linking COVID-19 and the incidence of venous thromboembolism (VTE), necessitating the inclusion of VTE prophylaxis in COVID-19 in-patient treatment guidelines (31). This would explain the increase in use of anticoagulants from post-wave 1 in our study population. We also observed the consistent use of colchicine throughout the pandemic at this hospital, despite it being shown to have no benefit by the National Department of Health (39)

Of the 39 HCW admissions reported in our study, HCWs were more likely to be hospitalized during pre-wave 1 (8; 5.26%), with the proportion of hospitalized HCW cases decreasing as the pandemic progressed. This was most likely due to increased awareness of the disease as more information about COVID-19 became available and the enforced infection prevention control protocols. The most affected HCW cadres during the study period were nurses (21 cases; 53.85%), which is different from findings in other settings where doctors had the highest risk of COVID-19 exposure compared with nurses, with this risk increasing as exposure to respiratory aerosols increased (40). Our findings could be explained by the fact that nurses generally tend to work for longer periods in close contact with patients compared to doctors (41,42). As frontline workers, HCW have been recognized as being at high risk of COVID-19 infection, with issues such as availability and proper use of personal protective equipment, workplace setting and type of exposure contributing to the overall risk of infection (40). A systematic review and meta-analysis reported that during the first 6 months of the pandemic, the prevalence of hospital admissions amongst HCW was 15.1% while mortality was 1.5% (40).

In our study, people of other race were more likely, while people of Indian descent were less likely to be hospitalized during the second wave. There was no association of race with mortality. This may indicate the presence of other underlying protective factors yet to be identified amongst such patients, that may prevent adverse clinical outcomes despite higher rates of hospitalization. Studies in the USA and UK have reported an association between race and ethnicity and the likelihood of a positive COVID-19 status and COVID-19 related hospitalization (43). Similarly, an association between non-White races and increased COVID-19 related mortality has also been found in South Africa (9).

The strength of our study is the large and comprehensive dataset that allowed us to identify important factors associated with admissions in the different pandemic waves as well as in-hospital mortality. There were significant missing data regarding patient signs and symptoms on admission, and because clinical records were not reviewed, we could not account for the missing data.

Conclusions

This study confirmed that older age, being male, having an existing comorbidity as well as infection during the second compared to the first wave were all factors associated with COVID-19 in-hospital mortality. These findings support the need to promote prevention strategies such as vaccination and stricter adherence to NPIs amongst individuals who have these risk factors in order to prevent high mortality rates during future waves of infection. The data would also be helpful in informing more specific management strategies amongst patients with these risk factors, including early referral and prioritization of treatment. Since the more transmissible beta variant has been suggested to contributed to the increased in-hospital mortality during the second wave, studies that will collect patient-level virus variant data and determine the relationship between in-hospital mortality and virus variants are required.

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