

# Hyperglycaemia, diabetes mellitus and COVID-19 in a tertiary hospital in KwaZulu-Natal

AS Ikram<sup>a</sup> and S Pillay<sup>b</sup>

<sup>a</sup>King Edward VIII Hospital, Durban, South Africa

<sup>b</sup>King Edward VIII Hospital, Nelson R Mandela School of Clinical Medicine, Durban, South Africa

\*Correspondence: [ahmedsameerikram@gmail.com](mailto:ahmedsameerikram@gmail.com), [drspillay@iafrica.com](mailto:drspillay@iafrica.com)



**Background:** Despite a substantial diabetes mellitus (DM) burden, there are few data regarding the relationship between DM and hyperglycaemia on COVID-19 severity and outcome in African populations. This study aimed to describe this relationship in the local context, and to determine whether our data correlated with observations made globally.

**Methods:** Retrospective analysis of patients admitted to King Edward VIII Hospital with COVID-19 during June–September 2020 was undertaken. The sample was subdivided into three cohorts: DM; hyperglycaemia only (HO); and neither DM nor hyperglycaemia (NDNH). Patients living with DM (PLWD) were further subdivided into those with hyperglycaemia (PLWDH) versus normoglycaemia (PLWDN). Comparisons were made across groups.

**Results:** The 236 participants enrolled comprised 79 with DM, 22 with HO, and 135 with NDNH. Half of patients with HO, 26.6% of PLWD and 15.6% of NDNH died. A log-rank test revealed significantly lower survival rates for those with HO compared with PLWDN ( $p = 0.001$ ) and NDNH ( $p = 0.002$ ). PLWDH also had significantly lower survival rates when compared with these two groups ( $p = 0.018$  and  $p = 0.039$  respectively). PLWD were significantly more likely to receive steroids (odds ratio [OR] 2.03) and oxygen therapy (OR 2.93). Patients with HO were significantly more likely to receive mechanical ventilation (MV) (OR 7.7) and die (OR 5.43). Compared with PLWDN, PLWDH were significantly more likely to receive MV (OR 10.83) and die (OR 4.24). When compared with PLWDN, patients with HO were significantly more likely to receive oxygen (100% vs. 70.4%), MV (63.6% vs. 3.7%) or die (50% vs. 11.1%).

**Conclusion:** This study concurred with global findings, highlighting the importance of glycaemia as a prognostic marker in patients hospitalised with COVID-19. We recommend that all patients admitted with COVID-19 have a random glucose on admission and strict glycaemic control in those with hyperglycaemia to improve outcomes.

**Keywords:** diabetes, diabetes mellitus, hyperglycaemia, COVID-19, South Africa, Africa

## Introduction

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has seized the attention of the world having been declared a global pandemic – contributing to millions of deaths globally, massive socioeconomic decline and widespread unrest.<sup>1</sup> Patients affected by SARS-CoV-2 experience varying degrees of disease severity and clinical outcome – most notably influenced by advanced age and comorbid chronic medical conditions.<sup>2</sup> Diabetes mellitus (DM) is one such condition that has been shown to dramatically influence outcome in patients affected with COVID-19.<sup>3,4</sup> This is consistent with observations made in two previous coronavirus outbreaks – Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) – which demonstrated more severe disease and higher mortality rates in patients living with DM (PLWD).<sup>5–7</sup> However, data on this association, from South Africa and Africa, have been scarce despite the dire prognostic implications.

A bidirectional relationship has been observed: whilst DM increases the risk of severe disease and mortality, infection with COVID-19 has also led to worsened glycaemic control and hyperglycaemic crises in patients with pre-existing DM, and even heralded new-onset DM in others.<sup>8</sup> Interestingly, even in patients without DM, hyperglycaemia has been observed to be an independent risk factor for severe disease and poor outcome in patients with COVID-19.<sup>8–10</sup> Conversely,

adequate glycaemic control appears to be associated with more favourable outcomes – potentially serving as a means of intervention to prevent severe disease in these patients.<sup>6,7,11</sup>

China has provided some of the first observational studies regarding the impact of DM on COVID-19 outcome. According to a large case-series report conducted in China, 5.3% of the total 72 314 COVID-19 patients had DM and, in comparison with other chronic medical conditions like hypertension, DM was associated with a higher mortality rate.<sup>12,13</sup> Likewise, an early case-series report in Seattle revealed that 58% of critically ill patients with COVID-19 had DM.<sup>14</sup> Another retrospective study in China showed that patients with DM and uncontrolled hyperglycaemia had more severe disease, higher mortality rates, and required more intensive in-hospital management.<sup>11</sup> Similarly, a retrospective observational study comprising 1 122 patients with COVID-19 from 88 US hospitals revealed that patients with DM and/or uncontrolled hyperglycaemia had a longer duration of hospital stay and higher fatality rates (28.8%) when compared with controls (6.2%).<sup>15</sup> Interestingly, patients with uncontrolled hyperglycaemia and no DM were noted to have higher mortality rates compared with patients with DM – further supporting the hypothesis that acute hyperglycaemia may be an independent risk factor for poor clinical outcome in COVID-19.<sup>15</sup>

From an African perspective, the burden of DM is especially prominent in the sub-Saharan region, having killed approximately

370 000 people in 2019, with projections estimating a 48% growth in the number of adults with DM by 2030 – far exceeding the expected rise globally.<sup>12,16,17</sup> Moreover, it is estimated that approximately 60% of patients with DM in Africa remain undiagnosed – the highest of all countries affiliated with the International Diabetes Federation (IDF).<sup>17,18</sup> The African population is unique in a variety of ways. First, a number of atypical subtypes of DM have been identified in populations predominantly of African origin, which include ketosis-prone diabetes and fibrocalculous diabetes.<sup>16,19</sup> Second, in contrast to European populations, type 1 DM in people from sub-Saharan Africa has a later age of onset (15–19 and 22–29 years, respectively), and African patients are more likely to develop microvascular complications in comparison with Caucasians.<sup>16,20</sup> There is a paucity of data regarding the true burden of DM in South Africa. However, according to the most recent 2019 IDF estimates, South Africa had the highest prevalence of DM (ages 20–79) in Africa, with approximately 4.6 million individuals affected, as well as the highest number of deaths attributable to DM in 2019 – approximately 89 800 casualties.<sup>17</sup> DM contributes to approximately 58 deaths daily and is the fifth highest cause of natural death in South Africa.<sup>18</sup> Despite its late arrival, COVID-19 has now firmly established itself as a major cause for concern in South Africa with an excess of 2.2 million cases and more than 66 000 deaths as of this writing.<sup>21</sup>

Whilst it is generally accepted that DM increases the risk of severe disease and worse clinical outcome, there appear to be a number of variables influencing this association. Taking into consideration the HIV and tuberculosis burden, atypical forms of DM, socioeconomic status of the population and healthcare limitations, how does South Africa compare? Our study aimed to describe the relationship between hyperglycaemia and DM on disease severity and clinical outcome in patients hospitalised with COVID-19 at a tertiary hospital in KwaZulu-Natal (KZN); and secondarily to determine whether our data correlated with observations made globally.

## Methods

### Study design and setting:

This was a retrospective observational study conducted at King Edward VIII Hospital (KEH) – one of the tertiary hospitals situated in KZN, South Africa.

### Participants:

All patients older than 13 years of age who were hospitalised to KEH with laboratory-confirmed SARS-CoV-2 infection during the period June 1, 2020–September 31, 2020 were included in the study sample. Key exclusion criteria included patients without an admission random blood glucose available, those with a low admission glucose (< 3 mmol/l) and all pregnant patients.

### Data collection

Ethics approval for this study was obtained from the local ethics review committee (University of KwaZulu-Natal Biomedical Research and Ethics Committee – BREC/00002069/2020) and the Department of Health, together with appropriate site approval prior to commencement.

Data were accessed from the medical records of participants and the following information obtained:

- Basic demographics – age, gender, race;
- Pre-existing or newly diagnosed DM;

- Admission random capillary glucose;
- Admission vital signs – respiratory rate, oxygen saturation;
- Laboratory results – white cell count (WCC), C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, D-dimer;
- Presence of co-morbidities;
- Treatment received – oxygen, steroids, mechanical ventilation;
- Duration of hospital stay;
- Outcome – discharged home, down referred, up referred to higher level of care, died.

The obtained data were then analysed as per the aims of the study.

### Statistical analysis

The data collected were analysed with SPSS version 27.0 (IBM Corp, Armonk, NY, USA) and Stata version 16.0 (StataCorp, College Station, TX, USA). Categorical data were presented as frequencies and percentages and compared utilising chi-square tests. Odds ratios (OR) were used as a measure of association. Descriptive statistics (mean and standard deviation) were used to describe the quantitative data that were collected. Continuous variable group means were compared using unpaired t-tests for normally distributed data. Kaplan–Meier analysis was performed to represent time to death for each cohort graphically, and a log-rank test performed to assess the difference between the various cohorts. A *p*-value of < 0.05 was regarded as statistically significant.

### Study procedure

Included patients were organised into three cohorts based on the presence or absence of DM and admission hyperglycaemia, as outlined below:

1. Patients living with DM (PLWD) – either pre-existing or newly diagnosed (this was subdivided into those with normoglycaemia and those with admission hyperglycaemia);
2. Patients with admission hyperglycaemia but with no history of DM (hyperglycaemia only [HO]);
3. Patients without evidence of DM or admission hyperglycaemia (neither DM nor hyperglycaemia [NDNH]).

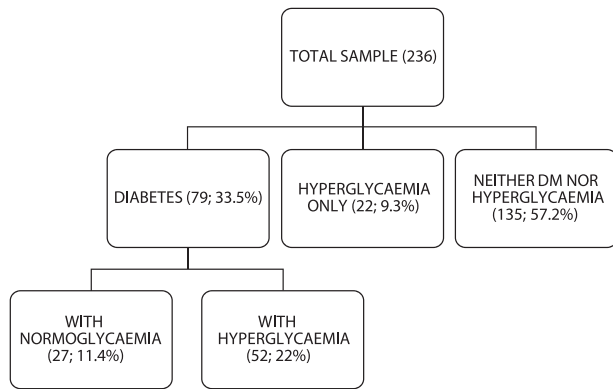
Patients with NDNH served as a control group for comparison against those with DM and HO.

### Definitions

COVID-19 infection was defined by a positive SARS-CoV-2 PCR laboratory result. Pre-existing DM was defined as those patients with a history of DM and already on oral and/or insulin anti-diabetes treatment on admission, whereas newly diagnosed DM was defined as an absence of a history of DM and an admission HbA1c > 6.5%.<sup>22</sup> HO was defined by a random capillary glucose of > 10 mmol/l on admission with no history of DM (HbA1c < 6.5% or not tested during period of hospital stay).<sup>23</sup> Patients with NDNH were defined as those with an admission random glucose of < 10 mmol/l and with no history of DM (HbA1c < 6.5%). The *total hyperglycaemia* population included those with HO plus the DM with hyperglycaemia cohort (Figure 1).

### Outcome measures

The following outcome variables were used to assess disease severity and outcome:



**Figure 1:** Study sample subdivisions.

- Clinical features of COVID-19 severity (moderate-severe disease):<sup>24</sup>
  - Admission oxygen saturation (< 94% on room air);
  - Respiratory rate (> 24 breaths/minute).
- Laboratory features of COVID-19 severity (moderate-severe disease):<sup>25–28</sup>
  - White cell count (>  $11 \times 10^9/l$ );
  - CRP (> 40 mg/l);
  - LDH (> 300 U/l);
  - D-dimer (> 0.5 mg/l);
  - Ferritin (> 500 ng/ml).
- Treatment received (intervention required correlating with more severe disease):
  - No treatment;
  - Required oxygen;
  - Required steroids;
  - Required mechanical ventilation.
- Duration of hospital stay (days):
  - Longer duration of stay correlating with more severe disease.
- Outcome:
  - Discharged home;
  - Down referred;
  - Up referred to a higher level of care;
  - Died.

## Results

### Demographics

A total of 236 patients were enrolled in the study. Of the total cohort, significantly more patients were female ( $n = 141/236$ , 59.7%;  $p = 0.003$ ) and Black African ( $n = 207/236$ , 87.7%;  $p < 0.001$ ). Most patients fell within the 40–69 years age categories ( $n = 142/236$ , 60.17%;  $p < 0.001$ ).

The total cohort comprised 79 (33.47%) PLWD, 22 (9.32%) with HO with no history of DM, and 135 (57.2%) with NDNH. The majority of PLWD had hyperglycaemia on admission (65.82% vs. 34.18%,  $p = 0.005$ ). The DM cohort comprised a significantly greater number of patients with pre-existing DM (78.48% vs. 21.52%,  $p < 0.001$ ).

Of the total cohort, 40.3% ( $n = 95/236$ ) of patients had coexisting hypertension ( $p = 0.003$ ), while 28.8% ( $n = 68/236$ ) of patients had comorbid HIV infection ( $p < 0.001$ ). The majority of PLWD had comorbid hypertension as well ( $n = 55/79$ , 69.62%;  $p < 0.001$ ) (Table 1).

### Clinical features of severity

Most patients from the total cohort had an oxygen saturation > 94% ( $n = 131/236$ , 56.7%;  $p = 0.041$ ) and a respiratory rate < 24 breaths/minute ( $n = 189/236$ , 80.1%;  $p < 0.001$ ). Similarly, the majority of patients with NDNH had an oxygen saturation > 94% ( $n = 92/134$ , 68.7%;  $p < 0.001$ ). In contrast, the bulk of patients with HO had a low oxygen saturation ( $n = 18/22$ , 81.8%;  $p = 0.003$ ), as well as over half of those in the PLWD cohort ( $n = 40/75$ , 53.3%;  $p = 0.564$ ) (Table 2).

### Laboratory features of severity

Table 2 demonstrates that, of the total cohort, significantly more patients had a WCC  $< 11 \times 10^9/l$ , a CRP > 40 mg/l and a LDH > 300 U/l ( $p < 0.001$ ). Patients with HO had the greatest proportion of patients with an elevated WCC, CRP and LDH (40.9%, 100% and 100% respectively) in comparison with the DM (25%, 85.3% and 85.7% respectively) and NDNH cohorts (17.1%, 61.8% and 85.2% respectively). With regard to an elevated D-dimer, significantly more patients had DM ( $n = 28/58$ , 51.85%;  $p = 0.001$ ) compared with the other two cohorts (Table 2).

### Treatment received

Most patients received steroids ( $n = 160/236$ , 67.8%;  $p < 0.001$ ) and oxygen therapy ( $n = 166/236$ , 70.3%;  $p < 0.001$ ), while considerably fewer patients received mechanical ventilation ( $n = 55/235$ , 23.4%;  $p < 0.001$ ). More intensive in-hospital treatment was observed in those with HO and DM versus those with NDNH. Among those with HO, all patients received oxygen ( $n = 22/22$ , 100%;  $p < 0.001$ ), while 95.5% received steroids ( $n = 21/22$ ;  $p < 0.001$ ), and approximately two-thirds received mechanical ventilation ( $n = 14/22$ , 63.6%;  $p = 0.201$ ). In comparison with those with NDNH, patients with DM had a greater proportion of patients receiving steroids (74.7%; 59/79), oxygen (81%; 64/79) and mechanical ventilation (20.5%; 16/68) (Table 2).

### Outcomes

From the total cohort, 53 (22.5%) patients died ( $p < 0.001$ ), with the highest mortality rate observed in those with HO. Half of those with HO ( $n = 11/22$ , 50%), 26.6% ( $n = 21/79$ ) of PLWD, and 15.6% ( $n = 21/135$ ) of those with NDNH, died. In contrast, patients with NDNH had significantly more patients who were discharged home ( $n = 39$ , 28.9%) in comparison with the DM and HO cohorts (16.5% and 0% respectively) ( $p < 0.001$ ) (Table 2).

### Comparisons between DM with hyperglycaemia vs DM with normoglycaemia vs HO cohorts

Of the DM cohort ( $n = 79$ ), 52 patients (65.8%) had hyperglycaemia, whereas 27 (34.2%) had normoglycaemia on admission. In addition, there were 22 patients with admission HO with no history of DM. Table 3 demonstrates that PLWD with hyperglycaemia presented more frequently with clinical and laboratory features of severe disease compared with those PLWD with normoglycaemia, and those with HO. Comparisons between patients with HO versus PLWD with normoglycaemia revealed the following significant findings:

- More patients with HO had an oxygen saturation < 94% (81.8% vs. 42.3%;  $p = 0.014$ ) and a respiratory rate > 24 breaths/minute (27.3% vs. 14.8%;  $p = 0.016$ ).

**Table 1:** Demographic data

	Total patients <i>n</i> (%)	PLWD		Patients with HO <i>n</i> (%)	Patients with NDNH <i>n</i> (%)	<i>p</i> -value
		With hyperglycaemia <i>n</i> (%)	With normoglycaemia <i>n</i> (%)			
Gender:						
Male	95 (40.3)	27 (51.9)	6 (22.2)	9 (40.9)	53 (39.3)	< 0.001
Female	141 (59.7)	25 (48.1)	21 (77.8)	13 (59.1)	82 (60.7)	< 0.001
<i>p</i> -value	0.003	0.782	0.004	0.394	0.013	
Race:						
Black African	207 (87.7)	42 (80.8)	23 (85.2)	19 (86.4)	123 (91.1)	< 0.001
Asian	20 (8.5)	6 (11.5)	3 (11.1)	2 (9.1)	9 (6.7)	0.112
White	8 (4.4)	4 (7.7)	1 (3.7)	1 (4.5)	2 (1.5)	0.392
Coloured	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.7)	0.392
<i>p</i> -value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	
Age (years):						
10–19	5 (2.1)	0 (0)	0 (0)	0 (0)	5 (3.7)	0.002
20–29	21 (8.9)	0 (0)	1 (3.7)	0 (0)	20 (14.8)	< 0.001
30–39	27 (11.4)	3 (5.8)	3 (11.1)	1 (4.5)	20 (14.8)	< 0.001
40–49	43 (18.2)	10 (19.2)	2 (7.4)	4 (18.2)	27 (20)	< 0.001
50–59	50 (21.2)	15 (28.8)	5 (18.5)	5 (22.7)	25 (18.5)	< 0.001
60–69	49 (20.8)	12 (23.1)	8 (29.6)	9 (40.9)	20 (14.8)	0.064
70–79	29 (12.3)	10 (19.2)	4 (14.8)	2 (9.1)	13 (9.6)	0.012
80–89	9 (3.8)	2 (3.8)	4 (14.8)	0 (0)	3 (2.2)	0.274
90–99	3 (1.3)	0 (0)	0 (0)	1 (4.5)	2 (1.5)	0.3
<i>p</i> -value	< 0.001	< 0.001	0.021	< 0.001	< 0.001	
HIV infection						
Yes	68 (28.8)	11 (21.2)	5 (18.5)	5 (22.7)	47 (34.8)	< 0.001
No	168 (71.2)	41 (78.8)	22 (81.5)	17 (77.3)	88 (65.2)	< 0.001
<i>p</i> -value	< 0.001	< 0.001	0.001	0.011	< 0.001	
Asthma/COPD						
Yes	12 (5.1)	2 (3.8)	3 (11.1)	1 (4.5)	6 (4.4)	0.198
No	224 (94.9)	50 (96.2)	24 (88.9)	21 (95.5)	129 (95.6)	< 0.001
<i>p</i> value	<0.001	< 0.001	< 0.001	< 0.001	< 0.001	
Hypertension						
Yes	95 (40.3)	35 (67.3)	20 (74.1)	10 (45.5)	30 (22.2)	0.001
No	141 (59.7)	17 (32.7)	7 (25.9)	12 (54.5)	105 (77.8)	< 0.001
<i>p</i> -value	0.003	0.013	0.012	0.67	< 0.001	
Chronic kidney disease						
Yes	18 (7.6)	6 (11.5)	4 (14.8)	2 (9.1)	6 (4.4)	0.485
No	218 (92.4)	46 (88.5)	23 (85.2)	20 (90.9)	129 (95.6)	< 0.001
<i>p</i> value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	

- More patients with HO had a WCC > 11 × 10<sup>9</sup>/l (40.9% vs. 7.4%; *p* = 0.002).
- More patients with HO received steroids (95.5% vs. 69.3%; *p* < 0.001), oxygen (100% vs. 70.4%; *p* < 0.001) and mechanical ventilation (63.6% vs. 3.7%; *p* = 0.002).
- A significantly greater number of patients with HO died (50% vs. 11.1%; *p* = 0.005) or were up referred to a higher level of care (36.4% vs. 0%; *p* = 0.023) (Table 3).

#### Comparisons between total patients with hyperglycaemia (with/without DM) vs. total patients with normoglycaemia

Of the total cohort, 74 patients had hyperglycaemia (with or without DM) – 52 patients with DM, and 22 with HO – with the remainder (*n* = 162) having normoglycaemia on admission.

Comparison between those with hyperglycaemia (with/without DM) and those with normoglycaemia revealed significant

differences in disease severity and outcome. Significantly more patients with hyperglycaemia had a low oxygen saturation (*n* = 47, 66.2%; *p* = 0.006), received steroids (*n* = 64, 86.5%; *p* < 0.001) and received oxygen (*n* = 67, 90.5%; *p* < 0.001). In addition, more patients with hyperglycaemia received mechanical ventilation and died; however, this was not significant.

With regard to outcome, most patients with hyperglycaemia died (*n* = 29/74, 39.2%) compared with other outcome variables (*p* < 0.001), whereas the majority of patients with normoglycaemia were either down referred (*n* = 77/162, 47.5%) or discharged home (*n* = 45/162, 27.8%) (*p* < 0.001).

#### Odds of clinical features of severity, laboratory features of severity, treatment intervention and outcomes: comparison between the various subgroups

Table 4 defines the relationships present between the various subgroups and severity of disease, treatment interventions and outcomes.

**Table 2:** Clinical and laboratory features of severity, treatment received and outcome

Frequency (n) and percentage (%) of patients with/who		All patients n (%)	PLWD n (%)	Patients with HO n (%)	Patients with NDNH n (%)	p-value
Oxygen saturation (O <sub>2</sub> ) < 94%	Yes	100 (43.3)	40 (53.3)	18 (81.8)	42 (31.3)	0.005
	No	131 (56.7)	35 (46.7)	4 (18.2)	92 (68.7)	< 0.001
p-value		0.041	0.564	0.003	< 0.001	
Respiratory rate > 24/minute	Yes	47 (19.9)	19 (24.1)	6 (27.3)	22 (16.3)	0.001
	No	189 (80.1)	60 (75.9)	16 (72.7)	113 (83.7)	< 0.001
p-value		< 0.001	< 0.001	0.033	< 0.001	
WCC > 11 x 10 <sup>9</sup> /l	Yes	50 (22)	19 (25)	9 (40.9)	22 (17.1)	0.062
	No	177 (78)	57 (75)	13 (59.1)	107 (82.9)	< 0.001
p-value		< 0.001	< 0.001	0.394	< 0.001	
CRP > 40 mg/l	Yes	143 (73.3)	58 (85.3)	17 (100)	68 (61.8)	< 0.001
	No	52 (26.7)	10 (14.7)	0 (0)	42 (38.2)	< 0.001
p value		< 0.001	< 0.001	< 0.001	0.013	
LDH > 300 U/l	Yes	48 (87.3)	18 (85.7)	7 (100)	23 (85.2)	0.015
	No	7 (12.7)	3 (14.3)	0 (0)	4 (14.8)	0.156
p-value		< 0.001	0.001	0.008	< 0.001	
D-dimer > 0.5 mg/l	Yes	54 (58.7)	28 (68.3)	6 (50)	20 (51.3)	0.001
	No	38 (41.3)	13 (31.7)	6 (50)	19 (48.7)	0.035
p-value		0.095	0.019	1	0.873	
Ferritin > 500 ng/ml	Yes	5 (55.6)	2 (66.7)	0 (0)	3 (50)	0.247
	No	4 (44.4)	1 (33.3)	0 (0)	3 (50)	0.174
p-value		0.739	0.564	0.135	1	
Received steroids	Yes	160 (67.8)	59 (74.7)	21 (95.5)	80 (59.3)	< 0.001
	No	76 (32.2)	20 (25.3)	1 (4.5)	55 (40.7)	< 0.001
p value		< 0.001	< 0.001	< 0.001	0.031	
Received oxygen	Yes	166 (70.3)	64 (81)	22 (100)	80 (59.3)	< 0.001
	No	70 (29.7)	15 (19)	0 (0)	55 (40.7)	< 0.001
p-value		< 0.001	< 0.001	< 0.001	0.031	
Received ventilation	Yes	55 (23.4)	16 (20.5)	14 (63.6)	25 (18.5)	0.154
	No	180 (76.6)	62 (79.5)	8 (36.4)	110 (81.5)	< 0.001
p-value		< 0.001	< 0.001	0.201	< 0.001	
Died		53 (22.5)	21 (26.6)	11 (50)	21 (15.6)	0.152
Up referred		29 (12.3)	5 (6.3)	8 (36.4)	16 (11.9)	0.035
Down referred		102 (43.2)	40 (50.6)	3 (13.6)	59 (43.7)	< 0.001
Discharged home		52 (22)	13 (16.5)	0 (0)	39 (28.9)	< 0.001
p-value		< 0.001	< 0.001	0.004	< 0.001	

Figure 2 demonstrates difference in survival rates among those with DM with hyperglycaemia, DM with normoglycaemia, HO and NDNH. The lowest survival rates were seen in those with HO, whereas the highest were seen in those with DM and normoglycaemia. A log-rank test revealed significantly lower survival rates for those with HO compared with those with DM and normoglycaemia ( $p = 0.001$ ) and those with NDNH ( $p = 0.002$ ). Additionally, those with DM and hyperglycaemia also had significantly lower survival rates compared with those with DM and normoglycaemia ( $p = 0.018$ ) and those with NDNH ( $p = 0.039$ ). The mean survival time was 11.78 days for those with HO (95% CI 6.85–16.7); 16.74 days for those with DM and hyperglycaemia (95% CI 11.81–21.67); 17.31 days for those with NDNH (95% CI 15.73–18.88); and 24.87 days for those with DM and normoglycaemia (95% CI 11.81–21.67).

## Discussion

Our study concurred with global findings and emphasised the adverse effects of DM and hyperglycaemia on disease severity and outcome in patients admitted with COVID-19. In addition,

hyperglycaemia alone was found to be an independent risk factor for severe disease and adverse outcomes – even more so than a diagnosis of DM.

DM and hyperglycaemia have been shown to adversely affect outcome in patients hospitalised with COVID-19.<sup>3,4,8–10</sup> Thus, one may be able to extrapolate that populations with a high burden of diabetes ought to have higher COVID-19-related fatality rates. However, this finding is not universal. Despite what may be expected, given the high burden of DM in India, the Indian population has a comparatively low mortality rate compared with other countries (1.3%).<sup>12,29</sup> Thus, there appear to be other factors influencing this association. Furthermore, in the United States, racial and ethnic minorities have been disproportionately affected by COVID-19, with approximately 30% of cases occurring in Hispanic/Latino populations and approximately 12% in Black Americans.<sup>30,31</sup> Although the exact reason for these incongruences remains to be determined, it possibly suggests a racial or genetic component. Studies investigating this association have been conducted globally, and are not



**Table 3:** Comparisons between DM with hyperglycaemia vs. DM with normoglycaemia vs. Hyperglycaemia Only cohorts

Factor			DM with hyperglycaemia n (%)	DM with normoglycaemia n (%)	HO with no DM n (%)	p-value
Gender	Male		27 (51.9)	6 (22.2)	9 (40.9)	< 0.001
	Female		25 (48.1)	21 (77.8)	13 (59.1)	0.15
p-value			0.782	0.004	0.394	
Race	Black African		42 (80.8)	23 (85.2)	19 (86.4)	0.005
	Asian		6 (11.5)	3 (11.1)	2 (9.1)	0.307
	White		4 (7.7)	1 (3.7)	1 (4.5)	0.223
	Coloured		0 (0)	0 (0)	0 (0)	-
p-value			< 0.001	< 0.001	< 0.001	
Age (years)	10–19		0 (0)	0 (0)	0 (0)	-
	20–29		0 (0)	1 (3.7)	0 (0)	0.368
	30–39		3 (5.8)	3 (11.1)	1 (4.5)	0.565
	40–49		10 (19.2)	2 (7.4)	4 (18.2)	0.039
	50–59		15 (28.2)	5 (18.5)	5 (22.7)	0.018
	60–69		12 (23.1)	8 (29.6)	9 (40.9)	0.639
	70–79		10 (19.2)	4 (14.8)	2 (9.1)	0.039
	80–89		2 (3.8)	4 (14.8)	0 (0)	0.135
	90–99		0 (0)	0 (0)	1 (4.5)	0.368
	p-value			< 0.001	0.021	< 0.001
Frequency (n) and percentage (%) of patients with:	HIV	Yes	11 (21.2)	5 (18.5)	5 (22.7)	0.18
		No	41 (78.8)	22 (81.5)	17 (77.3)	0.002
	p-value		< 0.001	0.001	0.011	
	Asthma/COPD	Yes	2 (3.8)	3 (11.1)	1 (4.5)	0.607
		No	50 (96.2)	24 (88.9)	21 (95.5)	< 0.001
	p-value		< 0.001	< 0.001	< 0.001	
	Hypertension	Yes	35 (67.3)	20 (74.1)	10 (45.5)	< 0.001
		No	17 (32.7)	7 (25.9)	12 (54.5)	0.125
	p-value		0.013	0.622	0.67	
	Chronic kidney disease	Yes	6 (11.5)	4 (14.8)	2 (9.1)	0.368
		No	46 (88.5)	23 (85.2)	20 (90.9)	0.001
	p-value		< 0.001	< 0.001	< 0.001	
Frequency (n) and percentage (%) of patients with:	Oxygen saturation (O <sub>2</sub> ) < 94%	Yes	29 (59.2)	11 (42.3)	18 (81.8)	0.014
		No	20 (40.8)	15 (57.7)	4 (18.2)	0.006
	p-value		0.199	0.433	0.003	
	Respiratory rate > 24/minute	Yes	15 (28.8)	4 (14.8)	6 (27.3)	0.016
		No	37 (71.2)	23 (85.2)	16 (72.7)	0.011
	p-value		0.002	< 0.001	0.033	
Frequency (n) and percentage (%) of patients with:	WCC > 11 x 10 <sup>9</sup> /l	Yes	17 (34.7)	2 (7.4)	9 (40.9)	0.002
		No	32 (65.3)	25 (92.6)	13 (59.1)	0.019
	p-value		0.032	< 0.001	0.394	
	CRP > 40 mg/l	Yes	40 (88.9)	18 (78.3)	17 (100)	0.001
		No	5 (11.1)	5 (21.7)	0 (0)	0.082
	p-value		< 0.001	0.007	< 0.001	
	LDH > 300 U/l	Yes	12 (92.3)	6 (75)	7 (100)	0.289
		No	1 (7.7)	2 (25)	0 (0)	0.368
	p-value		0.002	0.157	0.008	
	D-dimer > 0.5 mg/l	Yes	17 (70.8)	11 (64.7)	6 (50)	0.069
		No	7 (29.2)	6 (35.3)	6 (50)	0.949
	p-value		0.041	0.225	1	
	Ferritin > 500 ng/ml	Yes	1 (100)	1 (50)	0 (0)	0.368
		No	0 (0)	1 (50)	0 (0)	0.368

(Continued)

Table 3: Continued.

Factor			DM with hyperglycaemia n (%)	DM with normoglycaemia n (%)	HO with no DM n (%)	p-value
	p-value		0.317	1	-	
Frequency (n) and percentage (%) of patients who:	Received steroids	Yes	43 (82.7)	16 (59.3)	21 (95.5)	< 0.001
		No	9 (17.3)	11 (40.7)	1 (4.5)	0.018
	p-value		< 0.001	0.336	< 0.001	
	Received oxygen	Yes	45 (86.5)	19 (70.4)	22 (100)	< 0.001
		No	7 (13.5)	8 (29.6)	0 (0)	0.022
	p-value		< 0.001	0.034	< 0.001	
	Received ventilation	Yes	15 (29.4)	1 (3.7)	14 (63.6)	0.002
		No	36 (70.6)	26 (96.3)	8 (36.4)	< 0.001
	p-value		0.003	< 0.001	0.201	
Frequency (n) and percentage (%) of patients who:	Died		18 (34.6)	3 (11.1)	11 (50)	0.005
		Up referred	5 (9.6)	0 (0)	8 (36.4)	0.023
	Down referred		22 (42.3)	18 (66.7)	3 (13.6)	< 0.001
	Discharged home		7 (13.5)	6 (22.2)	0 (0)	0.037
	p-value		0.001	< 0.001	0.004	

necessarily generalisable to the local context given the heterogeneity of the population. To the best of our knowledge, this is the first study evaluating the association between DM, hyperglycaemia and COVID-19 in a South African population.

Our study demonstrated that patients with DM were significantly more likely to have a low oxygen saturation, an elevated CRP, receive steroids and oxygen therapy, and were less likely to be discharged home, compared with those with NDNH. Furthermore, hyperglycaemia itself was noted to be an independent risk factor for disease severity and mortality, even in those without a history of DM. These patients were significantly more likely to have a low oxygen saturation; elevated WCC and CRP; received steroids, oxygen and mechanical ventilation; and die compared with those without DM or hyperglycaemia. Interestingly, patients with hyperglycaemia alone fared worse than those with DM and normoglycaemia – with significantly greater odds of having a low oxygen saturation; an elevated WCC; receiving steroids, oxygen and mechanical ventilation; and death. This suggests that glycaemia may be even more important than a diagnosis of DM as a predictor of prognosis. This is in keeping with findings by Bode *et al.*, who demonstrated higher mortality rates in patients with diabetes and/or uncontrolled hyperglycaemia. Additionally, worse outcomes were also noted in those with uncontrolled hyperglycaemia compared with those with DM.<sup>15</sup>

The importance of glycaemia is further demonstrated when analysing the DM cohort. The DM *with* hyperglycaemia cohort was significantly more likely to have an elevated WCC, receive steroids and mechanical ventilation, and die compared with those with DM and normoglycaemia. This concurs with findings by Zhu *et al.* demonstrating a lower incidence of leucocytosis, steroid therapy, mechanical ventilation and death in those with DM and well-controlled glucose, compared with those with DM and poorly controlled glucose.<sup>11</sup> In the total cohort of patients with hyperglycaemia (those with and without DM), there existed significantly higher odds of an increased respiratory rate and lower oxygen saturation on admission; an elevated WCC and CRP; steroid and oxygen use and mechanical

ventilation; and mortality (vs. those with normoglycaemia, with and without DM). These patients with hyperglycaemia were also significantly less likely to be discharged home, again highlighting the role of glycaemia and its resultant influence on patient outcomes.

Seventeen patients in the study were newly diagnosed with DM during their admission, of whom six (35%) died (vs. 24.2% of those with pre-existing DM). This was an unexpected finding, as one would expect patients with pre-existing DM, often of more advanced age and with established micro- and/or macrovascular complications, to have poorer outcomes. A possible explanation is that these newly diagnosed patients were not on treatment previously and were more likely to have hyperglycaemia on admission. Additionally, these patients may be presenting at advanced stages of their disease, possibly reflecting the greater burden of undiagnosed DM in the general population. This brings to the fore the need for implementation of effective population screening protocols.

Hyperglycaemia has been postulated to cause more severe disease and worse outcomes in those with COVID-19.<sup>7,9–11,15</sup> Glycosylation of the ACE-2 receptor is needed for linkage of the SARS-CoV-2 virus to the cell receptor. Therefore, hyperglycaemia is thought to support cellular entry of the virus, in addition to generating an inflated inflammatory response.<sup>7,9,10</sup> This process of glycosylation, however, has been shown to be reversible during the early phases, thus hypothesising that prompt normalisation of blood glucose during this acute phase may lessen the degree of inflammation and ACE-2 binding capacity of the virus, potentially averting a more severe form of the disease.

We recommend that all patients hospitalised with COVID-19 have a random blood glucose performed on admission, as well as prompt active management of hyperglycaemia. The intended benefit is threefold. First, it may serve as a prognostic marker for severe disease and poorer outcome. Second, in those patients identified with hyperglycaemia, active glycaemic control measures can then be implemented to potentially

**Table 4:** Odds ratios (OR) for clinical and laboratory features of severity, treatment received, and outcome - comparison between various subgroups

Factor	OR	95% CI	p-value
<b>DM vs. NDNH:</b>			
Respiratory rate > 24 breaths/minute	1.63	0.817–3.24	0.167
Oxygen saturation < 94%	2.5	1.4–4.48	0.002
WCC > 11 x 10 <sup>9</sup> /l	1.62	0.81–3.24	0.172
CRP > 40 mg/l	3.58	1.65–7.76	0.001
LDH > 300 U/l	1.04	0.21–5.27	0.959
D-dimer > 0.5 mg/l	2.05	0.82–5.08	0.123
Received steroids	2.03	1.1–3.74	0.024
Received oxygen	2.93	1.52–5.67	0.001
Received ventilation	1.14	0.564–2.288	0.722
Died	1.97	0.99–3.89	0.052
Discharged home	0.48	0.24–0.98	0.043
<b>HO vs. NDNH</b>			
Respiratory rate > 24 breaths/minute	1.93	0.68–5.47	0.218
Oxygen saturation < 94%	9.86	3.14–30.92	< 0.001
WCC > 11 x 10 <sup>9</sup> /l	3.37	1.28–8.85	0.014
CRP > 40 mg/l	21.72	1.27–370.6	0.034
LDH > 300 U/l	2.87	0.14–59.76	0.496
D-dimer > 0.5 mg/l	0.95	0.26–3.47	0.938
Received steroids	14.44	1.89–110.51	0.01
Received oxygen	31.02	1.84–522.21	0.017
Received ventilation	7.7	2.92–20.34	< 0.001
Died	5.43	2.09–14.13	0.001
Discharged home	0.05	0.003–0.92	0.043
<b>DM with hyperglycaemia vs. DM with normoglycaemia:</b>			
Respiratory rate > 24 breaths/minute	2.33	0.69–7.89	0.174
Oxygen saturation < 94%	1.98	0.75–5.19	0.166
WCC > 11 x 10 <sup>9</sup> /l	6.64	1.4–31.47	0.017
CRP > 40 mg/l	2.22	0.57–8.65	0.249
LDH > 300 U/l	4	0.3–53.47	0.295
D-dimer > 0.5 mg/l	1.32	0.35–5	0.678
Received steroids	3.28	1.15–9.4	0.027
Received oxygen	2.71	0.86–8.53	0.089
Received ventilation	10.83	1.35–87.25	0.025
Died	4.24	1.12–16	0.033
Discharged home	0.54	0.16–1.82	0.324
<b>Newly diagnosed DM vs. pre-existing DM:</b>			
Respiratory rate > 24 breaths/minute	1.43	0.43–4.75	0.561
Oxygen saturation < 94%	2	0.61–6.55	0.252
WCC > 11 x 10 <sup>9</sup> /l	2.74	0.86–8.71	0.087
CRP > 40 mg/l	1.27	0.24–6.71	0.776
LDH > 300 U/l	3.64	0.16–81.71	0.416
D-dimer > 0.5 mg/l	1.33	0.29–6.15	0.712
Received steroids	3.07	0.64–14.81	0.163
Received oxygen	4.67	0.57–38.35	0.152
Received ventilation	2.78	0.83–9.27	0.096
Died	1.71	0.54–5.41	0.362
Discharged home	1.81	0.48–6.82	0.379

(Continued)

**Table 4:** Continued.

Factor	OR	95% CI	p-value
<b>Total hyperglycaemia vs. total normoglycaemia:</b>			
Respiratory rate > 24 breaths/minute	2.07	1.07–4	0.03
Oxygen saturation < 94%	3.95	2.19–7.14	< 0.001
WCC > 11 x 10 <sup>9</sup> /l	3.18	1.66–6.09	< 0.001
CRP > 40 mg/l	6.23	2.34–16.61	< 0.001
LDH > 300 U/l	3.93	0.44–35.29	0.222
D-dimer > 0.5 mg/l	1.43	0.6–3.37	0.418
Received steroids	4.4	2.11–9.19	< 0.001
Received oxygen	6.09	2.63–14.11	< 0.001
Received ventilation	3.45	1.84–6.47	< 0.001
Died	3.71	1.96–7.01	< 0.001
Discharged home	0.27	0.12–0.64	0.003
<b>HO vs. DM with normoglycaemia:</b>			
Respiratory rate > 24 breaths/minute	2.16	0.52–8.89	0.288
Oxygen saturation < 94%	6.14	1.62–23.29	0.008
WCC > 11 x 10 <sup>9</sup> /l	8.65	1.63–46.08	0.011
CRP > 40 mg/l	10.41	0.53–202.41	0.122
LDH > 300 U/l	5.77	0.23–143.38	0.285
D-dimer > 0.5 mg/l	0.55	0.12–2.46	0.43
Received steroids	14.44	1.69–123.7	0.015
Received oxygen	19.62	1.06–363.23	0.045
Received ventilation	45.5	5.15–401.73	< 0.001
Died	8	1.85–34.54	0.005
Discharged home	0.07	0.004–1.39	0.082

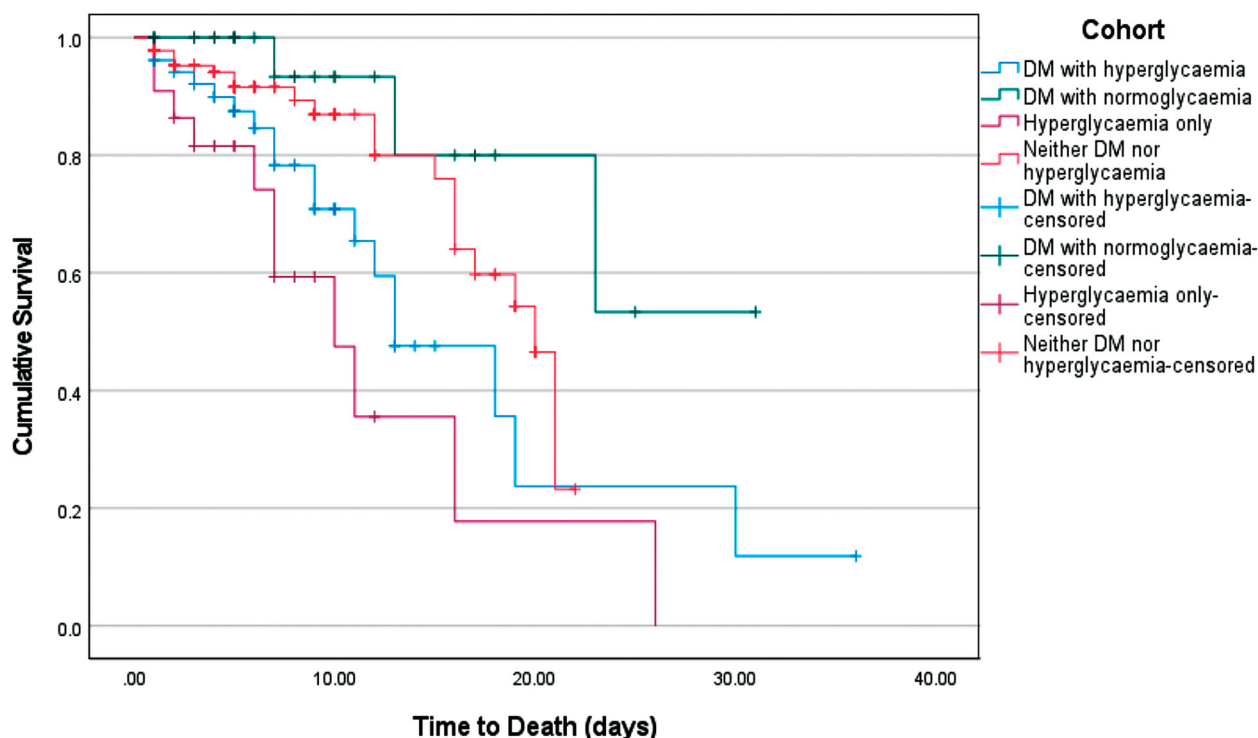
avert the associated adverse consequences. Lastly, those patients with hyperglycaemia (and no history of DM) can be screened for DM – and more so if other risk factors are present. Further studies of such nature with larger cohorts need to be conducted to assess the strength of this association, as well as the effects of pre-hospital and in-hospital glycaemic control on COVID-19 outcomes in African populations. Additionally, although it has been suggested that COVID-19 may precipitate new-onset DM in the acute setting, there is a paucity of data regarding the long-term effects of this virus on glycaemic status.<sup>8</sup> In this regard, further studies investigating the long-term effects will be forthcoming.

Despite this study focusing on the influence of DM and hyperglycaemia on COVID-19, it also highlights the reciprocal nature of this relationship. As a result of the COVID-19 outcry, numerous countries, including South Africa, have implemented strict lockdown strategies to curb the spread of this virus. Patients with DM have subsequently experienced greater difficulty accessing chronic medication as well as less frequent medical reviews, with the subsequent potential for worsened glycaemic control – which, in itself, is a risk factor for micro- and macrovascular complications and mortality. This is of significant concern given the fact that the estimated prevalence of DM in South Africa is the highest in the African continent.<sup>4</sup> Although not a primary aim, this study will also hopefully herald prioritisation of this chronic condition in the public healthcare sector.

### Study limitations

Due to the inhomogeneous nature of patients, numerous factors (other medical co-morbidities other than DM, advanced





**Figure 2:** Kaplan–Meier survival analysis: time to death (days) for each cohort.

age etc.) may also influence disease course and outcome. Because of the retrospective nature of this study, it was not possible to assess whether appropriate glycaemic control measures would have improved outcomes. Furthermore, not all patients had *all* laboratory markers of severity performed on admission – in particular ferritin, LDH and D-dimer – thus limiting its significance as a marker of severity in this study.

### Conclusion

DM and hyperglycaemia have been shown to adversely affect outcomes in patients hospitalised with COVID-19. Despite a substantial DM burden, there is a dearth of data regarding this relationship from African populations. This study concurred with global findings suggesting that DM and hyperglycaemia are both independent risk factors for severe disease and poor outcomes in patients hospitalised with COVID-19. Moreover, it was demonstrated that glycaemia may be even more important than a diagnosis of DM in terms of prognosis – with significantly lower survival rates in those with *hyperglycaemia alone* and *DM with hyperglycaemia* compared with the *DM with normoglycaemia* cohort. We recommend that all patients admitted with COVID-19 have a glucose measurement performed on admission, together with prompt active management of hyperglycaemia to improve outcomes. Further studies with larger cohorts need to be conducted to assess the strength of this association in African populations, as well as to assess the effect of inpatient glycaemic control on disease course.

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