Latent class analysis: an innovative approach for identification of clinical and laboratory markers of disease severity among COVID-19 patients admitted to the intensive care unit

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ABSTRACT

Objective: The aim of this study was to identify clinical and laboratory phenotype distribution patterns and their usefulness as prognostic markers in COVID-19 patients admitted to the intensive care unit (ICU) at Tygerberg Hospital, Cape Town.

Methods and results: A latent class analysis (LCA) model was applied in a prospective, observational cohort study. Data from 343 COVID-19 patients were analysed. Two distinct phenotypes (1 and 2) were identified, comprising 68.46% and 31.54% of patients, respectively. The phenotype 2 patients were characterized by increased coagulopathy markers (D-dimer, median value 1.73 ng/L vs 0.94 ng/L; $p < 0.001$), end-organ dysfunction (creatinine, median value 79 μmol/L vs 69.5 μmol/L; $p < 0.003$), under-perfusion markers (lactate, median value 1.60 mmol/L vs 1.20 mmol/L; $p < 0.001$), abnormal cardiac function markers (median N-terminal pro-brain natriuretic peptide (NT-proBNP) 314 pg/ml vs 63.5 pg/ml; $p < 0.001$ and median high-sensitivity cardiac troponin (Hs-TropT) 39 ng/L vs 12 ng/L; $p < 0.001$), and acute inflammatory syndrome (median neutrophil-to-lymphocyte ratio 15.08 vs 8.68; $p < 0.001$ and median monocyte value 0.68×10^9/L vs 0.45×10^9/L; $p < 0.001$).

Conclusion: The identification of COVID-19 phenotypes and sub-phenotypes in ICU patients could help as a prognostic marker in the day-to-day management of COVID-19 patients admitted to the ICU.

1. Introduction

The clinical spectrum of COVID-19 ranges from asymptomatic infection to severe pneumonia with respiratory failure and death (WHO, 2020). Many studies have reported on the clinical and laboratory characteristics of COVID-19 (Bastug et al., 2020; Parohan et al., 2020; Williamson et al., 2020; Kim et al., 2021; Zemlin et al., 2022). In 2020, the critical emphasis was on identifying and assessing distinct risk factors associated with COVID-19 mortality (Parohan et al., 2020; Williamson et al., 2020).

A retrospective study conducted in the USA showed that patients who were admitted with COVID-19 could be grouped according to two distinct phenotypes that were associated with mortality (Teng et al., 2021). In the first group patients were older, with several comorbidities and a higher mortality rate. In the second group, patients were younger, more likely to be obese, and male, with higher levels of the inflammatory markers — specifically C-reactive protein (CRP) and alanine aminotransferase (Teng et al., 2021). In contrast, another study found that SARS-CoV-2 infected females phenotypically had lower levels of CRP, serum creatinine, and D-dimer markers (Lusczek et al., 2021). A retrospective study conducted in Spain reported that patients with COVID-19 could be categorized into three distinct phenotypes (Gutiérrez-Gutiérrez et al., 2021). The first group comprised young patients who were less frequently male, with moderate viral symptoms and normal inflammatory parameters (Azoulay et al., 2020). The second group comprised patients with obesity, lymphocytopenia, and inflammatory parameters that were not excessively elevated. The third group comprised older patients with several comorbidities and higher inflammatory parameter levels than the second group (Gutiérrez-Gutiérrez et al., 2021). Similar phenotypes were reported in France among patients who were admitted to the intensive care unit (ICU) (Azoulay et al., 2020). An extensive literature review did not find any evidence of similar research conducted in Africa on COVID-19 phenotypes. African studies assessing COVID-19 outcomes showed that gender, age, inflammatory proteins, cardiac function, and coagulation parameters constitute potential COVID-19 phenotypes (Nachega et al., 2020; Dalal et al., 2021; Allwood et al., 2022; Zemlin et al., 2022). However, it remains unclear whether similar phenotypes exist in South Africa, due to different mortality rates and comorbidities.

Among COVID-19 deaths, the characteristics and underlying pathophysiology of each phenotypic group appear to be distinct (Teng et al., 2021). Hence, the identification of different phenotypes and subphenotypes of COVID-19 may provide guidance for basic, clinical, and translational research in sub-Saharan Africa. Due to the diversity of populations across the world, a broad understanding might allow clinicians and researchers to develop customized therapy, which may result in reduced mortality rates among severe COVID-19 patients (Teng et al., 2021). To our knowledge, there is little evidence on the phenotypic profiles of COVID-19 ICU patients in sub-Saharan Africa (Goswami et al., 2021). Our study aimed to identify clinical and laboratory phenotype distribution patterns and their usefulness as prognostic markers in COVID-19 patients admitted to the ICU in South Africa.

2. Methods

2.1. Study design

This prospective cohort study was conducted at Tygerberg Hospital (TBH) during the first two waves of the COVID-19 pandemic, between March 27, 2020 and February 10, 2021. TBH is a 1380-bed facility that serves as the main teaching hospital for Stellenbosch University Faculty of Medicine and Health Sciences. It provides a tertiary care service for around 3.5 million people. TBH was designated as a centre for COVID-19 management, with additional critical care facilities.

2.2. Study population and sample size

The study included data for 343 adult patients admitted with severe COVID-19 pneumonia to the designated ICU during the above-mentioned waves. Diagnosis was confirmed by a positive SARS-CoV-2 polymerase chain reaction (PCR) (Figure 1). A sample of 300 or more cases were desirable in order to reveal classes with low memberships and without poor functioning fit indices and convergence failures (Nylund-Gibson et al., 2022). Details regarding ICU admission criteria are documented in the Western Cape Government's provincial guidelines (Critical Care Society of Southern Africa, 2020).

2.3. Data collection

Clinical data were extracted from ICU clinical notes and entered onto a REDCap® (Research Electronic Data Capture, Stellenbosch, South Africa) database — a secure web application. Laboratory data were imported from the National Health Laboratory Service (NHLS) Laboratory Information System (TrakCare® Lab Enterprise) onto the REDCap database. Data quality assurance was undertaken by the research assistants and later verified by the supervisor of the research team, to ensure data quality prior to analysis. Detailed information on the clinical parameters is provided in previously published articles (Zemlin et al., 2022).

2.4. Statistical analysis

Class-defining variables for latent class identification included baseline demographic features as well as clinical and laboratory data. Continuous variables were reported as median and IQR (non-normal), and categorical variables as percentages. All variables with missing data were excluded from further analysis.

A multivariate mixture model was used to identify two distinct latent classes based on the variables of interest. A binomial response distribution was used for binary categorical variables and a Gaussian response distribution for continuous variables. These variables were centred and scaled to unit variance prior to model inference. Continuous variables that were skewed were log-transformed prior to analysis.

Data were allocated to the latent class based on the posterior model probability (probability of class assignment > 50%). The Wilcoxon rank sum was used to compare the median differences between the two identified classes for continuous variables. The Pearson chi-squared test was used for categorical variables.

A two-sided p-value < 0.05 was considered statistically significant. The two-class model was compared with a model including an additional latent class, based on model selection criteria (Akaike information criteria, AIC, and Bayesian information criteria, BIC), a likelihood ratio test, the size of the smallest class, the probability of class assignment, and qualitative evaluation of the defining class characteristics. BIC was used for parameterized Gaussian mixture models fitted by an expectation-maximization (EM) algorithm, initialized by model-based hierarchical clustering to obtain the number of latent classes. Integrated complete-data likelihood (ICL) was used to confirm the number of classes obtained using the BIC criteria.

The standardized means of continuous class-defining variables were compared to understand the clinical and biological characteristics that distinguished the two classes (Figures 2A–C), and raw data were compared by class. A sub-analysis was performed to assess whether there were any notable differences among the patients who died and those who were discharged. Stata (V.16, Stata Corp, College Station, Texas, USA) was used for data cleaning, and manipulation, and for the Wilcoxon and Pearson chi-squared tests, R (v.4.1.0, R Core Team) with R Studio (v.1.4.1, R Studio Team) was used for analysis in order to obtain the required number of classes.
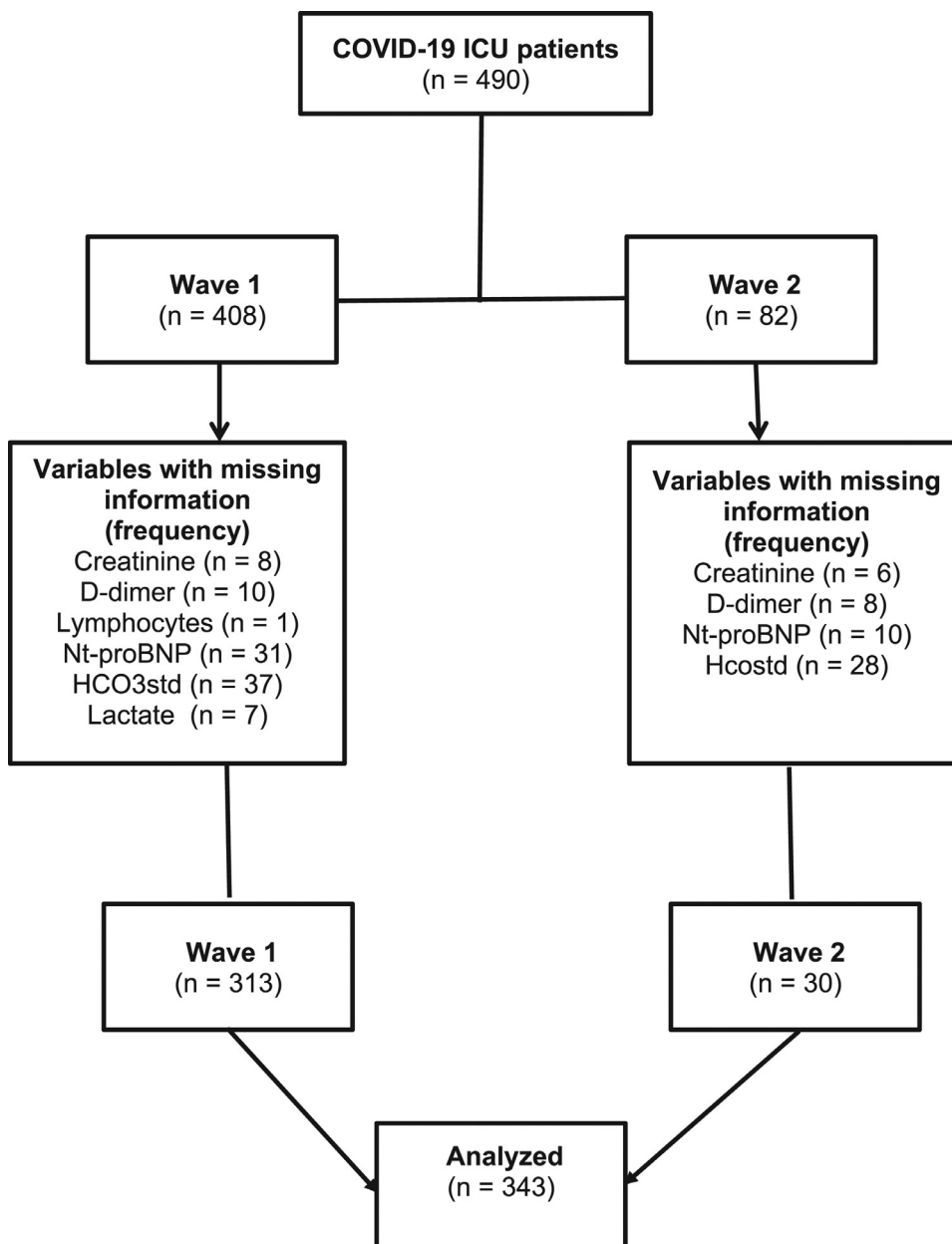
Figure 1. Consort diagram.

3. Results

The baseline characteristics of the cohort ($n = 343$) are presented in Table 1. The cohort had a slightly higher proportion of females ($n = 184$, 53.6%) and ICU mortality was high ($n = 216$, 63%). Two latent classes were identified, representing 75.8% (class 1, $n = 260$) and 24.2% (class 2, $n = 83$) of the cohort, respectively. Class 2 was notable primarily by the following: increased coagulopathy markers (D-dimer, median value 1.73 ng/L, IQR 0.61–5.70 for class 2 vs 0.94 ng/L, IQR 0.41–4.13 for class 1; $p < 0.001$); underperfusion markers (increased lactate — median value 1.60 mmol/L, IQR 1.10–2.10 for class 2 vs 1.20 mmol/L, IQR 1.00–1.40 for class 1; $p < 0.001$); end-organ dysfunction markers (creatinine — median value 79 μmol/L, IQR 65–110 for class 2 vs 69.5 μmol/L, IQR 56.5–83 for class 1; $p < 0.003$) — Table 2), cardiac function markers — NT-proBNP (median value 314 pg/ml, IQR 72–1346) for class 2 vs 63.5 pg/ml, IQR 32.5–193.5 for class 1; $p < 0.001$); Hs-TropT (median value 39 ng/L, IQR 13–102 for class 2 vs median value 12 ng/L, IQR 8–22 for class 1; $p < 0.001$ — Table 2); inflammatiry markers neutrophils-to-lymphocytes ratio (NLR — median value 15.08, IQR 8.75–24.41 for class 2 vs 8.68, IQR 5.71–14.21 for class 1; $p < 0.001$); and monocytes (median value 0.55×10^9/L, IQR 0.36–1.11 for class 2 vs 0.45×10^9/L, IQR 0.31–0.72 for class 1; $p = 0.011$ — Table 2).

In addition, females in class 2 had lower mean hemoglobin than those in class 1 (11.88 g/dL (1.75) vs 12.67 (1.37); $p = 0.014$). Similarly, the median pH value was lower in class 2 than in class 1 (7.36, IQR 7.30–7.43 vs 7.47, IQR 7.45–7.50; $p < 0.001$), and the median value HCO_3std was also lower in class 2 than in class 1 (23.05 mmol/L, IQR 19.70–25.60 vs 27.30 mmol/L, IQR 25.10–29.10; $p < 0.001$)). In contrast, the median value $PaCO_2$ was higher in class 2 than in class 1 (5.70 kPa, IQR 4.30–6.90 vs 4.80 kPa, IQR 4.30–5.30; $p < 0.001$).

When comparing class 2 patients with class 1 patients, the mortality risk was found to be 1.44 (95% CI 1.22–1.67); $p < 0.001$.

An optimum of two latent classes was obtained among the patients who died (Table 3). Class 2 was notable primarily due to increased values for: acute inflammatory syndrome (C-reactive protein — median value 194, IQR 133–307 for class 2 vs 153, IQR 100–247 for class 1; $p = 0.015$); NLR 12.53, IQR 7.34–22.56 for class 2 vs 9.50, IQR 6.21–15.16 for class 1; $p = 0.013$; and monocytes, median value 0.68×10^9/L,
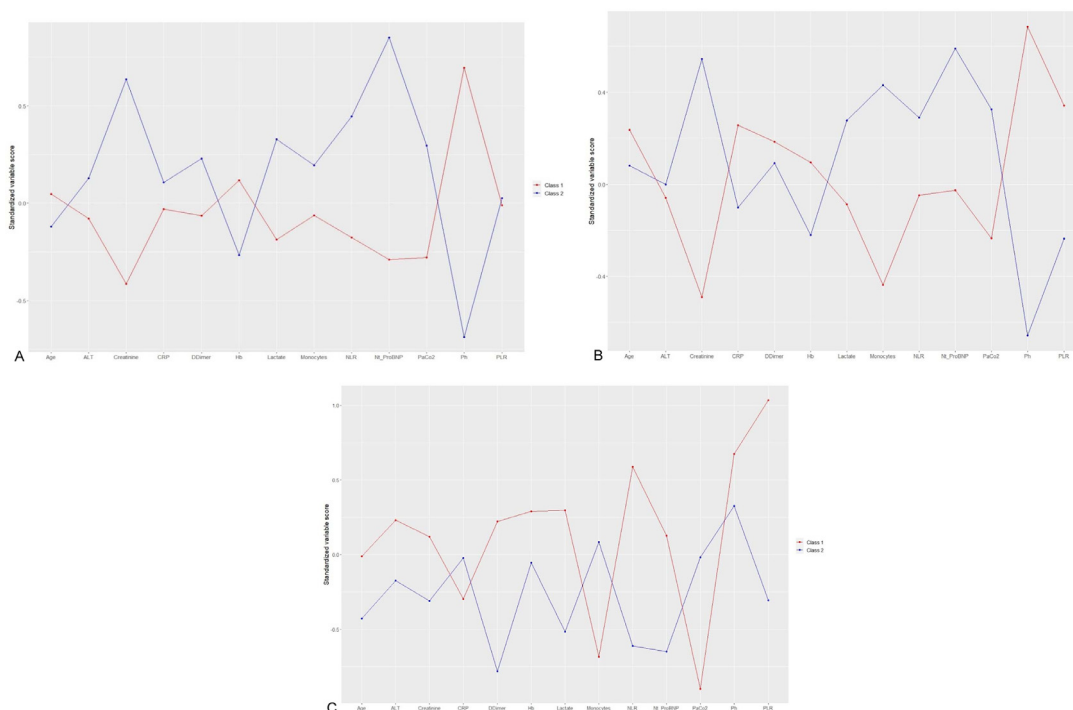
Figure 2. A: Differences in the mean standardized values of continuous class-defining variables by latent class among the ICU patients. . B: Differences in the mean standardized values of continuous class-defining variables by latent class among the patients who died. C: Differences in the mean standardized values of continuous class-defining variables by latent class among the patients who were discharged.

Table 1
Baseline clinical variables among the COVID-19 ICU study cohort.

Characteristic	*N*	Study cohort, median (IQR) or *n* (%)
Age (yrs)	343	55.56 (46.14–62.28)
Gender: female	343	184 (53.6%)
Diabetes mellitus	338	169 (50.0%)
Hypertension	338	204 (60.4%)
HIV positive	300	39 (13.0%)
ICU mortality	343	216 (63.0%)
Ventilation: non-invasive	343	294 (85.7%)
pH	343	7.46 (7.41–7.50)
PaCO$_2$	343	4.90 (4.30–5.60)
C-reactive protein	343	176.00 (109.00–270.00)
Neutrophils	343	9.92 (7.34–14.93)
Platelets	343	298.00 (231.00–373.00)
Nt-proBNP	343	303.00 (89.00–976.00)
Hemoglobin	343	13.20 (11.90–14.10)
Monocytes	343	0.48 (0.32–0.80)
D-dimer	343	1.09 (0.45–4.40)
Creatinine	343	77.00 (63.00–102.00)
Alanine aminotransferase (ALT)	343	33.00 (20.00–50.00)
Platelet/lymphocyte ratio	343	9.48 (6.15–16.71)
Neutrophil/lymphocyte ratio	343	285.06 (177.59–474.47)
Lactate	343	1.40 (1.10–1.90)
Hs-Troponin-T	343	13.00 (8.00–30.00)

Abbreviations: HIV: human immunodeficiency virus; PaCO$_2$: partial pressure of carbon dioxide; pH: potential of hydrogen; Nt-proBNP: N-terminal pro-brain natriuretic peptide.

IQR 0.39–2.70 for class 2 vs 0.45×10^9/L, IQR 0.30-0.68 for class 1; $p < 0.001$); underperfusion (increased lactate — median value 1.60 mmol/L, IQR 1.60–2.60 for class 2 vs 1.40 mmol/L, IQR 1.10–1.90 for class 1; $p = 0.021$), end-organ dysfunction (creatinine — median value 107 μmol/L, IQR 77–157 for class 2 vs 72 μmol/L, IQR 57–86 for class 1; $p < 0.001$ — Table 3); cardiac function — NT-proBNP (median value 784 pg/ml, IQR 217–2377 for class 2 vs 337 pg/ml, IQR 125–307 for class 1 ($p < 0.001$), Hs-TropT (median value 25 ng/L, IQR 12–62 for class 2 vs 14 ng/L, IQR 9–28 for class 1; $p < 0.001$ — Table 3). In

class 2, females had lower mean hemoglobin than in class 1 (11.96 g/dL (1.60) vs 12.60 g/dL (1.43); $p = 0.040$). Furthermore, the median pH and HCO$_3$std were lower in class 2 than in class 1 (7.37, IQR 7.30–7.44 vs 7.47, IQR 7.44–7.50; $p < 0.001$ and 23.55 mmol/L, IQR 20.00–25.90 vs 27.10 mmol/L, IQR 25.00–29.20; $p < 0.001$, respectively — Table 3). In contrast, the median PaCO$_2$ value was higher in class 2 than in class 1 (5.70 kPa, IQR 4.50–6.70 vs 4.90 kPa, IQR 4.30–5.30; $p < 0.001$ — Table 3). The platelet/lymphocyte ratio was found to be similar between class 2 and class 1 (247.31, IQR 70.59–475.51 vs 296.64, IQR 206.58–451.59; $p = 0.054$ — Table 3). The standardized means of continuous class-defining variables were compared among the patients who died, to understand the clinical and biological characteristics that distinguished the two classes (Figure 2B). Notable differences were observed between Figures 2A and 2B.

Figure 2C showed a different trend compared with that in Figure 2A, suggesting that what was observed overall was not what was observed among discharged patients (Figure 2A vs 2C). When comparing raw data by class among discharged patients, class 2 was notable primarily by increased values for: coagulopathy markers (D-dimer — median value 1.93 ng/L, IQR 0.55–5.12 for class 2 vs 0.40 ng/L, IQR 0.25–0.60 for class 1; $p < 0.001$); underperfusion markers (increased lactate — median value 1.60 mmol/L, IQR 1.10–2.10 for class 2 vs 1.20 mmol/L, IQR 1.00–1.40 for class 1; $p < 0.001$); end-organ dysfunction markers (creatinine — median value 79 μmol/L, IQR 65–110 for class 2 vs 69.5 μmol/L, IQR 56.5–83 for class 1; $p < 0.003$ — Table 4); cardiac function markers — NT-proBNP (median value 314 pg/ml, IQR 72–1346 for class 2 vs 63.5 pg/ml, IQR 32.5–193.5 for class 1; $p < 0.001$); Hs-TropT (median value 13 ng/L, IQR 9–36 for class 2 vs 6 ng/L, IQR 5–10.5 for class 1; $p < 0.001$ — Table 4); NLR (median value 12.39, IQR 6.48–20.29 for class 2 vs 6.67, IQR 4.51–9.00 for class 1; $p < 0.001$ — Table 4). Furthermore, the median PaCO$_2$ value was higher in class 2 than in class 1 (5.70 kPa, IQR 4.50–6.70 vs 4.90 kPa, IQR 4.30–5.30; $p < 0.001$). In contrast, the median HCO$_3$std value was lower in class 2 than in class 1 (23.55 mmol/L, IQR 20.00–25.90 vs 27.10 mmol/L, IQR 25.00–29.20; $p < 0.001$).

Table 2
Differences in clinical and laboratory characteristics between latent subclasses among COVID-19 ICU patients.

Characteristic	Reference intervals	Latent subclasses		p-value
		Class 1 (n = 260)	Class 2 (n = 83)	
Age (yrs)		55.87 (46.27–62.80)	53.98 (43.83–60.79)	0.28
Gender				0.25
Female		116 (44.6%)	43 (51.8%)	
Male		144 (55.4%)	40 (48.2%)	
Diabetes mellitus				0.37
		125 (48.6%)	44 (54.3%)	
Hypertension				0.98
Yes		155 (60.3%)	49 (60.5%)	
No		102 (39.7%)	32 (39.5%)	
HIV status				0.096
Positive		34 (14.8%)	5 (7.1%)	
Creatinine	49–90 μmol/L	72.00 (58.00–87.00)	112.00 (79.00–169.00)	< 0.001
D-dimer	0.00–0.25 mg/L	0.94 (0.41–4.13)	1.73 (0.61–5.70)	0.012
Hemoglobin	Male: 13.0–17.0 g/dL	13.69 (1.66)	13.24 (2.22)	0.301
	Female: 12.0–15.0 g/dL	12.67 (1.37)	11.88 (1.75)	0.014
Monocytes	0.30–0.80 × 10^9/L	0.45 (0.31–0.72)	0.55 (0.36–1.11)	0.011
NT-proBNP	< 125 pg/mL	219.00 (64.50–600.00)	1661.00 (362.00–4694.00)	< 0.001
Hs-TropT	< 100 ng/l	12.00 (8.00–22.00)	39.00 (13.00–102.00)	< 0.001
C-reactive protein	< 10 mg/L	176.00 (107.00–268.50)	200.00 (116.00–273.00)	0.39
pH	7.35–7.45	7.47 (7.45–7.50)	7.36 (7.30–7.43)	< 0.001
PaCO$_2$	4.26–6.38 kPa	4.80 (4.30–5.30)	5.70 (4.30–6.90)	< 0.001
Lactate	0.5–2.2 mmol/L	1.40 (1.00–1.80)	1.70 (1.20–3.30)	< 0.001
Alanine aminotransferase	7–40 U/L	31.00 (21.00–48.00)	37.00 (17.00–63.00)	0.33
HCO$_3$std	19–24 mmol/L	27.30 (25.10–29.10)	23.05 (19.70–25.60)	< 0.001
Neutrophil/lymphocyte ratio		8.68 (5.71–14.21)	15.08 (8.75–24.41)	< 0.001
Platelet/lymphocyte ratio		284.98 (179.11–451.85)	287.76 (154.87–584.13)	0.58

Table 3
Differences in clinical and laboratory characteristics between latent subclasses for COVID-19 ICU death patients.

Characteristic		Latent subclasses		p-value
		Class 1 (n = 135)	Class 2 (n = 81)	
Age (years)		57.77 (49.22–63.66)	57.07 (47.25–62.57)	0.52
Gender				0.48
Female		65 (48.1%)	43 (53.1%)	
Male		70 (51.9%)	38 (46.9%)	
Diabetes mellitus				0.27
Yes		68 (50.4%)	46 (58.2%)	
No		67 (49.6%)	33 (41.8%)	
Hypertension				0.65
Yes		83 (61.5%)	51 (64.6%)	
No		52 (38.5%)	28 (35.4%)	
HIV status				0.016
Positive		24 (18.5%)	3 (5.2%)	
Negative		106 (81.5%)	55 (94.8%)	
Creatinine	49–90 μmol/L	72.00 (57.00–86.00)	107.00 (77.00–157.00)	< 0.001
D-dimer	0.00–0.25 mg/L	1.43 (0.48–6.72)	1.33 (0.52–4.46)	0.52
Hemoglobin	Male: 13.0–17.0 g/dL;	13.73 (1.52)	13.44 (1.94)	0.469
	Female: 12.0–15.0 g/dL	12.60 (1.43)	11.96 (1.60)	0.040
Monocytes	0.30–0.80 × 10^9/L	0.45 (0.30–0.68)	0.68 (0.39–2.70)	< 0.001
NT-proBNP	< 125 pg/mL	337.00 (125.00–799.00)	784.00 (217.00–2377.00)	< 0.001
Hs-TropT	< 100 ng/l	14.00 (9.00–28.00)	25.00 (12.00–62.00)	< 0.001
C-reactive protein	< 10 mg/L	194.00 (133.00–307.00)	153.00 (100.00–247.00)	0.015
pH	7.35–7.45	7.47 (7.44–7.50)	7.37 (7.30–7.44)	< 0.001
PaCO$_2$	4.26–6.38 kPa	4.90 (4.30–5.30)	5.70 (4.50–6.70)	< 0.001
Lactate	0.5–2.2 mmol/L	1.40 (1.10–1.90)	1.60 (1.20–2.60)	0.021
Alanine aminotransferase	7–40 U/L	31.00 (22.00–47.00)	34.00 (17.00–51.00)	0.91
HCO$_3$std	19–24 mmol/L	27.10 (25.00–29.20)	23.55 (20.00–25.90)	< 0.001
Neutrophil/lymphocyte ratio		9.50 (6.21–15.16)	12.53 (7.34–22.56)	0.013
Platelet/lymphocyte ratio		296.64 (206.58–451.59)	247.31 (70.59–475.51)	0.054

4. Discussion

In this first study from Africa to report on clinical phenotypes associated with COVID-19, two distinct latent subclasses were identified, based on the patients' demographic, clinical, and laboratory profiles. The inflammatory syndrome, coagulopathy markers, underperfusion markers, end-organ dysfunction, and cardiac function markers were identified as statistically and clinically significant phenotypes. Aside

from the high HIV prevalence in the death sub-phenotype, demographics and comorbidities did not differ between the deceased and recovering sub-phenotypes in each sub-analysis. This implies that distinct COVID-19 progression pathways exist, and are independent of baseline risk factors for disease severity.

Our LCA showed that the class 2 phenotype, which accounted for 31.54% (83/343) of the total sample size, was associated with increased coagulopathy markers, end-organ dysfunction, underperfusion markers,

Table 4
Differences in clinical and laboratory characteristics between latent subclasses for COVID-19 ICU discharged patients.

Characteristic	Reference intervals	Latent subclasses		p-value
		Class 1 (n = 52)	Class 2 (n = 75)	
Age (years)		48.72 (39.46–58.43)	52.18 (43.75–60.51)	0.16
Gender				0.06
Female		26 (50%)	25 (33%)	
Male		26 (50%)	50 (67%)	
Diabetes mellitus				0.11
Yes		26 (53%)	29 (39%)	
No		23 (47%)	46 (61%)	
Hypertension				0.32
Yes		25 (51%)	45 (60%)	
No		24 (49%)	30 (40%)	
HIV status				0.55
Positive		5 (13%)	7 (9%)	
Negative		33 (87%)	67 (91%)	
Creatinine	49–90 μmol/L	69.50 (56.50–83.00)	79.00 (65.00–110.00)	0.003
D-dimer	0.00–0.25 mg/L	0.40 (0.25–0.60)	1.93 (0.55–5.12)	< 0.001
Hemoglobin	Male: 13.0–17.0 g/dL	13.62 (1.81)	13.49 (2.07)	0.500
	Female: 12.0–15.0 g/dL	13.08 (0.98)	12.26 (1.78)	0.122
Monocytes	0.30–0.80 $\times 10^9$/L	0.48 (0.29–1.94)	0.41 (0.32–0.62)	0.15
NT-proBNP	< 125 pg/mL	63.50 (32.50–193.50)	314.00 (72.00–1346.00)	< 0.001
Hs-TropT	< 100 ng/l	6.00 (5.00–10.50)	13.00 (9.00–36.00)	< 0.001
C-reactive protein	< 10 mg/L	151.50 (89.00–234.50)	176.00 (93.00–270.00)	0.31
pH	7.35–7.45	7.48 (7.46–7.50)	7.47 (7.42–7.51)	0.13
PaCO$_2$	4.26–6.38 kPa	4.90 (4.70–5.30)	4.40 (3.90–5.20)	< 0.001
Lactate	0.5–2.2 mmol/L	1.20 (1.00–1.40)	1.60 (1.10–2.10)	< 0.001
Alanine aminotransferase	7–40 U/L	32.50 (22.50–47.50)	33.00 (19.00–63.00)	0.46
HCO$_3$std	19–24 mmol/L	27.90 (27.10–29.20)	25.80 (23.20–28.00)	< 0.001
Neutrophil/lymphocyte ratio		6.67 (4.51–9.00)	12.39 (6.48–20.29)	< 0.001
Platelet/lymphocyte ratio		223.58 (53.94–368.61)	346.81 (234.65–530.00)	< 0.001

cardiac function markers, and acute inflammatory syndrome. Recent evidence suggests that altered coagulation is an important phenotypic marker in COVID-19-associated ARDS (Ranjeva et al., 2021). Ranjeva et al., demonstrated that the more severe phenotype was distinguished by significantly elevated D-dimer (Ranjeva et al., 2021). A high burden of thromboembolic disease was found among postmortem patients with severe COVID-19 infection (Nadkarni et al., 2020; Ranjeva et al., 2021). Furthermore, elevated baseline D-dimer among COVID-19 patients has been shown to predict major coagulation-associated complications, critical illness, and death (Al-Samkari et al., 2020; Ranjeva et al., 2021).

Several mechanisms have also been proposed to explain the association between NT-proBNP and Hs-TropT COVID-19 outcomes in the ICU. These include progressive inflammation, hypoxemia, sepsis, myocardial injury, and volume overload states, all of which can increase myocardial stress (Babapoor-Farrokhran et al., 2020; Kazory et al., 2020; Yoo et al., 2021; Bertini et al., 2022). COVID-19 vascular complications, such as pulmonary embolism and acute kidney injury, may aggravate myocardial stress. These mechanisms may characterize a cardiac function phenotype in COVID-19 patients admitted to the ICU (Yoo et al., 2021; Azevedo et al., 2021). This was demonstrated in our study by the presence of elevated NT-proBNP and Hs-TropT in the class 2 phenotype. The NLR is considered a surrogate marker of systemic hyperinflammation, and an independent predictor of poor outcome associated with COVID-19 (Li et al., 2020). In severe cases or among patients who died with COVID-19, the lymphocyte count was shown to have decreased progressively, while the neutrophil count gradually increased (Li et al., 2020).

Neutrophils are generally regarded as pro-inflammatory cells with a range of antimicrobial activities, which can be triggered by virus-related inflammatory factors, such as interleukin-6 and 8 (Li et al., 2020; Mangalmurti and Hunter, 2020). Similarly, a dysregulated monocyte response can be damaging to the host, as is seen in the macrophage activation syndrome induced by severe infections, including in infections with the related virus SARS-CoV-2 (Merad and Martin, 2020). Systematic inflammation triggered by SARS-CoV-2 significantly depresses cellular immunity, leading to a decrease in CD3+ T cells, CD4+ T cells, and CD8+ T cells (Li et al., 2020). As further clarified below, this patho-

physiology results in hypoinflammatory and hyperinflammatory states in class 2 and class 1, respectively.

Moderate anemia was also found to be a charateristic of class 2 phenotype. Wang et al. reported lower hemoglobin levels in patients with more severe COVID-19 (Wang et al., 2020). This anemia was probably due to hyperinflammatory processes associated with SARS-CoV-2 infection, while the normal mean Hb levels found in class 1 may have been due to a hypoinflammatory state.

In the sub-analyses that included COVID-19 mortality in the ICU, the class 2 phenotype had higher levels of acute-phase proteins associated with inflammation, end-organ dysfunction, underperfusion, and cardiac function markers than the class 1 phenotype. Furthermore, HIV-positive status was more prevalent in the class 1 phenotype than in the class 2 phenotype. Recent LCAs involving COVID-19 patients have revealed a hyperinflammatory syndrome among sub-phenotypes (da Silva et al., 2020; Wang et al., 2021), with markedly elevated CRP defining these sub-phenotypes, as demonstrated by our findings. In contrast, 62.5% (135/216) of the patients who died in the class 1 phenotype were hypoinflammatory. A plausible explanation for this may be viral cytotoxicity as a primary driver of mortality in the hypoinflammatory sub-phenotype, whereas excessive inflammation could be a primary driver of mortality in the hyperinflammatory sub phenotype, as evidenced by higher levels of pro-inflammatory markers and an increased prevalence of multiorgan failure (Sinha et al., 2021).

Hypoinflammatory factors may explain the mortality in the class 1 sub-phenotype in our study. In addition, those who died within class 1 had a high HIV prevalence of 18.5% (24/135). Indeed, SARS-CoV-2 and HIV may both decrease CD4 count and lymphocytes (Tamuzi et al., 2020), which could explain the hypoinflammatory sub-phenotype in class 1.

Our findings also revealed that class 2 was characterized by elevated lactate and creatinine levels. Two recent LCAs revealed that renal-morbidity and high-morbidity phenotypes had more in-hospital complications than the low-morbidity phenotype (da Silva et al., 2020; Ranjeva et al., 2021). Phenotypes have been associated with an increased risk of myocardial infarction, heart failure, and acute kidney

injury (Benítez et al., 2022). This could account for the high prevalence of acute coronary syndromes in sub-phenotype 2. Another study found that a subclass with kidney dysfunction and hyperinflammatory response, defined by renal failure (elevated serum creatinine), lymphopenia, and elevated CRP, had the highest likelihood of ICU transfer or in-hospital mortality when compared with other subclasses (Wang et al., 2021). Higher creatinine and lower platelet levels indicate that clinical worsening within the severe baseline stratum is caused by cell death, macrophage activation, and overt organ dysfunction, with disseminated intravascular coagulation (Webb et al., 2020; Su et al., 2021).

Discharged patients within class 2 (59.05%; 75/127) presented elevated coagulopathy markers, end-organ dysfunction, cardiac function markers, lymphocytes, and platelet counts in the sub-analyses. D-dimer was found to be positively associated with CRP, serum ferritin, procalcitonin (PCT), and interleukin (IL)-2R in this study (Long et al., 2020). This shows that moderately elevated D-dimer may be associated with an inflammatory syndrome in the survived patients sub-phenotype in class 2, potentially improving the prognosis of COVID-19 patients. Furthermore, moderately elevated D-dimer may be associated with a less severe cytokine storm, as observed in the mortality sub-analyses. D-dimer does not directly stimulate IL-6 — the key factor inducing a cytokine storm, which is associated with mortality caused by sepsis or septic shock (Eljilany and Elzouki, 2020). It can also be hypothesized that use of prophylaxis for thromboembolism may have been more effective in the survived sub-phenotypes of classes 1 and 2.

End-organ failure has been reported following hospital discharge with COVID-19 (Ayoubkhani et al., 2021). COVID-19 pathogenesis and multiple-organ injury include direct virus-induced cytotoxicity in angiotensin-converting enzyme 2 (ACE2)-expressing cells, renin-angiotensin-aldosterone system (RAAS) dysregulation due to virus-mediated ACE2 downregulation, immune response dysregulation, endothelial cell injury, thrombo-inflammation, and tissue fibrosis (Gupta et al., 2020; Lopes-Pacheco et al., 2021). It can be reasonably speculated that the high survival rate in sub-phenotype 2 was due to a milder phenotype of COVID-19 organ failure. This is also true for sub-phenotype 2's elevated cardiac function markers and acute coronary syndrome. Even though sub-phenotype 1 was characterized by organ failure, D-dimer was < 1.0 μg/mL on admission, which has been associated with a lower risk of fatality (Chen et al., 2020; Eljilany et al., 2020; Guan et al., 2020; Tang et al., 2020; Zhou et al., 2020; Lopes-Pacheco et al., 2021).

To the best of our knowledge, this is Africa's first LCA to report the underlying phenotypes of COVID-19 patients admitted to the ICU. Our study demonstrated the benefit of evaluating prognostic markers within sub-phenotypes. The results may help in identifying groups of COVID-19 ICU patients who are at the highest risk of death and may benefit from additional clinical attention. Another advantage of this study was that it presented a phenotyping schema that divided COVID-19 ICU patients into less heterogeneous subgroups. However, inconsistency in case reporting, with 30% (147/490) of patients admitted to the ICU having missing data, may have impacted on data completeness. Further LCAs focusing on missing comorbidities, clinical symptoms, CD4 counts among HIV-infected patients, and therapies may also be important, with more informative profiles strengthening our phenotyping model.

5. Conclusion

In summary, our analysis identified two different phenotypes among COVID-19 patients admitted to the ICU. These two phenotypes were markedly different, characterized by increased coagulopathy markers, end-organ dysfunction, acute inflammatory syndrome, cardiac function markers, and underperfusion markers in phenotype 2. In the sub-analysis, the two sub-phenotypes were also found to differ, with increased acute inflammatory syndrome, end-organ dysfunction, cardiac function markers, and underperfusion in sub-phenotype 2. Among those who died, HIV-positive status was more prevalent in sub phenotype 1.

Among those who survived, the two sub-phenotypes were again different, with elevated coagulopathy markers, end-organ dysfunction, cardiac function markers, and acute coronary syndromes in sub-phenotype 2. Applying these different COVID-19 sub-phenotypes could help clinicians in day-to-day decision making, including the prognosis and management of COVID-19 patients admitted to the ICU.

Informed consent statement

The investigators obtained ethical approval and waiver of consent from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University and the Research Committee of Tygerberg Hospital.

Ethics

This study was approved by the Health Research Ethics Committee of Stellenbosch University, approval number: N20/04/002_COVID-19. Patient confidentiality was ensured by labelling data with unique episode numbers. The research project followed the established guidelines regarding the ethical conduct of studies involving human participants.

Availability of data and materials

Data are available upon reasonable request from the corresponding author.

Conflicts of interest

All authors declare no conflicts of interest.

CRediT authorship contribution statement

Lovemore N. Sigwadhi: Data curation, Formal analysis, Methodology, Writing – review & editing. **Jacques L. Tamuzi:** Writing – review & editing. **Annalise E. Zemlin:** Writing – review & editing. **Zivanai C. Chapanduka:** Investigation, Supervision, Writing – review & editing. **Brian W. Allwood:** Writing – review & editing. **Coenraad F. Koegelenberg:** Writing – review & editing. **Elvis M. Irusen:** Writing – review & editing. **Usha Lalla:** Writing – review & editing. **Veranyuy D. Ngah:** Data curation, Methodology, Writing – review & editing. **Anteneh Yalew:** Data curation, Writing – review & editing. **Perseverence Savieri:** Writing – review & editing. **Isaac Fwemba:** Writing – review & editing. **Thumeka P. Jalavu:** Writing – review & editing. **Rajiv T. Erasmus:** Writing – review & editing. **Tandi E. Matsha:** Writing – review & editing. **Alimuddin Zumla:** Investigation, Supervision, Writing – review & editing. **Peter S. Nyasulu:** Investigation, Methodology, Supervision, Writing – review & editing.

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References

Allwood BW, Koegelenberg CF, Ngah VD, Sigwadhi LN, Irusen EM, Lalla U, Yalew A, Tamuzi JL, McAllister M, Zemlin AE, Jalavu TP, Erasmus R, Chapanduka ZC, Matsha TE, Fwemba I, Zumla A, Nyasulu PS. COVID-19 Research Response Collaboration. Predicting COVID-19 outcomes from clinical and laboratory parameters in an intensive care facility during the second wave of the pandemic in South Africa. IJID Reg 2022;3:242–7.

Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ, Rosovsky RP. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020;136(4):489–500.

Azevedo RB, Botelho BG, Hollanda JVG, Ferreira LVL, Junqueira de Andrade LZ, Oei SSML, Mello TS, Muxfeldt ES. COVID-19 and the cardiovascular system: a comprehensive review. J Hum Hypertens 2021;35(1):4–11.

Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, Banerjee A. Post-COVID syndrome in individuals admitted to hospital with COVID-19: retrospective cohort study. BMJ 2021;372:n693.

Azoulay E, Zafrani L, Mirouse A, Lengliné E, Darmon M, Chevret S. Clinical phenotypes of critically ill COVID-19 patients. Intensive Care Med 2020;46(8):1651–2.

Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: possible mechanisms. Life Sci 2020;253.

Bastug A, Bodur H, Erdogan S, Gokcinar D, Kazancioglu S, Kosovali BD, Ozbay BO, Gok G, Turan IO, Yilmaz G, Gonen CC, Yilmaz FM. Clinical and laboratory features of COVID-19: predictors of severe prognosis. Int Immunopharmacol 2020;88.

Benítez ID, de Batlle J, Torres G, González J, de Gonzalo-Calvo D, Targa ADS, Gort–Paniello C, Moncusí-Moix A, Ceccato A, Fernández-Barat L, Ferrer R, Garcia-Gasulla D, Menéndez R, Motos A, Peñuelas O, Riera J, Bermejo-Martin JF, Peñasco Y, Ricart P, MC Martin Delgado, Aguilera L, Rodríguez A, Boado Varela MV, Suarez-Sipmann F, Pozo-Laderas JC, Solé-Violan J, Nieto M, Novo MA, Barberán J, Amaya Villar R, Garnacho-Montero J, García-Garmendia JL, Gómez JM, Lorente JÁ, Blandino Ortiz A, Tamayo Lomas L, López-Ramos E, Úbeda A, Catalán-González M, Sánchez-Miralles A, Martínez Varela I, Jorge García RN, Franco N, Gumucio-Sanguino VD, Huerta Garcia A, Bustamante-Munguira E, Valdivia LJ, Caballero J, Gallego E, Martínez de la Gándara A, Castellanos-Ortega Á, Trenado J, Marin-Corral J, Albaiceta GM, de la Torre MDC, Loza-Vázquez A, Vidal P, Lopez Messa J, Añón JM, Carbajales Pérez C, Sagredo V, Bofill N, Carbonell N, Socias L, Barberà C, Estella A, Valledor Mendez M, Diaz E, López Lago A, Torres A, Barbé F. CIBERESUCICOVID Project (COV20/00110, ISCIII). Prognostic implications of comorbidity patterns in critically ill COVID-19 patients: a multicenter, observational study. Lancet Reg Health Eur 2022;18.

Critical Care Society of Southern Africa. Allocation of scarce critical care resources during the COVID-19 pandemic health emergency in South Africa, 2020. https://criticalcare.org.za/wp-content/uploads/2020/04/Allocation-of-Scarce-Critical-Care-Resources-During-the-COVID-19-Public-Health-Emergency-in-South-Africa.pdf.

Bertini M, D'Aniello E, Di Ienno L, Gibiino F, Tavazzi G, Volta CA, Contoli M, Papi A, Campo G, Ferrari R, Rapezzi C. Phenotypic heterogeneity of COVID-19 pneumonia: clinical and pathophysiological relevance of the vascular phenotype. ESC Heart Fail 2022;9(1):263–9.

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13.

Dalal J, Triulzi I, James A, Nguimbis B, Dri GG, Venkatasubramanian A, Noubi Tchoupopnou Royd L, Botero Mesa S, Somerville C, Turchetti G, Stoll B, Abbate JL, Mboussou F, Impouma B, Keiser O, Coelho FC. COVID-19 mortality in women and men in sub-Saharan Africa: a cross-sectional study. BMJ Glob Health 2021;6(11).

da Silva JF, Hernandez-Romieu AC, Browning SD, Bruce BB, Natarajan P, Morris SB, Gold JAW, Neblett Fanfair R, Rogers-Brown J, Rossow J, Szablewski CM, Oosmanally N, D'Angelo MT, Drenzek C, Murphy DJ, Hollberg J, Blum JM, Jansen R, Wright DW, Sewell W, Owens J, Lefkove B, Brown FW, Burton DC, Uyeki TM, Patel PR, Jackson BR, Wong KK. COVID-19 clinical phenotypes: presentation and temporal progression of disease in a cohort of hospitalized adults in Georgia, United States. Open Forum Infect Dis 2020;8(1):ofaa596.

Eljilany I, Elzouki AN. D-Dimer, Fibrinogen, and IL-6 in COVID-19 patients with suspected venous thromboembolism: a narrative review. Vasc Health Risk Manag 2020;16:455–62.

Goswami N, Fredriksen PM, Lundin KEA, Agu C, Elias SO, Motaung KS, Brix B, Cvirn G, Sourij H, Stelzl E, Kessler HH, Salon A. Nkeh-Chungag B. COVID-19 and its effects on endothelium in HIV-positive patients in sub-Saharan Africa: cardiometabolic risk, thrombosis, and vascular function (ENDOCOVID STUDY). BMC Infect Dis 2021;21(1):719.

Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G,

Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS. China Medical Treatment Expert Group for COVID-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–20.

Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. Nat Med 2020;26(7):1017–32.

Gutiérrez-Gutiérrez B, Del Toro MD, Borobia AM, Carcas A, Jarrín I, Yllescas M, Ryan P, Pachón J, Carratalà J, Berenguer J, Arribas JR, J; Rodríguez-Baño. REIPI-SEIMC COVID-19 group and COVID@HULP groups. Identification and validation of clinical phenotypes with prognostic implications in patients admitted to hospital with COVID-19: a multicentre cohort study. Lancet Infect Dis 2021;21(6):783–92.

Kazory A, Ronco C, McCullough PA. SARS-CoV-2 (COVID-19) and intravascular volume management strategies in the critically ill. Proc (Bayl Univ Med Cent) 2020;0(0):1–6.

Kim L, Garg S, O'Halloran A, Whitaker M, Pham H, Anderson EJ, Armistead I, Bennett NM, Billing L, Como-Sabetti K, Hill M, Kim S, Monroe ML, Muse A, Reingold AL, Schaffner W, Sutton M, Talbot HK, Torres SM, Yousey-Hindes K, Holstein R, Cummings C, Brammer L, Hall AJ, Fry AM, Langley GE. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). Clin Infect Dis 2021;72(9):e206–14.

Li X, Liu C, Mao Z, Xiao M, Wang L, Qi S, Zhou F. Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic review and meta-analysis. Crit Care 2020;24(1):647.

Long X, Zhang Z, Zou W, Ling J, Li D, Jing L, Yu S, Zou X, Bian Y, Wu W, Li S, Fang M. Coagulopathy of patients with COVID-19 is associated with infectious and inflammatory markers. Risk Manag Healthc Policy 2020;13:1965–75.

Lopes-Pacheco M, Silva PL, Cruz FF, Battaglini D, Robba C, Pelosi P, Morales MM, Caruso Neves C, Rocco PRM. Pathogenesis of multiple organ injury in COVID-19 and potential therapeutic strategies. Front Physiol 2021;12.

Luscezek ER, Ingraham NE, Karam BS, Proper J, Siegel L, Helgeson ES, Lotfi-Emran S, Zolfaghari EJ, Jones E, Usher MG, Chipman JG, Dudley RA, Benson B, Melton GB, Charles A, Lupei MI, Tignanelli CJ. Characterizing COVID-19 clinical phenotypes and associated comorbidities and complication profiles. PLoS One 2021;16(3).

Mangalmurti N, Hunter CA. Cytokine storms: understanding COVID-19. Immunity 2020;53(1):19–25.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20(6):355–62.

Nachega JB, Ishoso DK, Otokoye JO, Hermans MP, Machekano RN, Sam-Agudu NA, Bongo-Pasi Nswe C, Mbala-Kingebeni P, Madinga JN, Mukendi S, Kolié MC, Nkwembe EN, Mbuyi GM, Nsio JM, Mukeba Tshialala D, Tshiasuma Pipo M, Ahuka-Mundeke S, Muyembe-Tamfum JJ, Mofenson L, Smith G, Mills EJ, Mellors JW, Zumla A, Mavungu Landu DJ, Kayembe JM. Clinical characteristics and outcomes of patients hospitalized for COVID-19 in Africa: early insights from the Democratic Republic of the Congo. Am J Trop Med Hyg 2020;103(6):2419–28.

Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno PR, Pujadas E, Arvind V, Bose S, Charney AW, Chen MD, Cordon-Cardo C, Dunn AS, Farkouh ME, Glicksberg BS, Kia A, Kohli-Seth R, Levin MA, Timsina P, Zhao S, Fayad ZA, Fuster V. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76(16):1815–26.

Nylund-Gibson K, Garber AC, Carter DB, Chan M, Arch DAN, Simon O, Whaling K, Tartt E, Lawrie SI. Ten frequently asked questions about latent transition analysis, 2022. https://psycnet.apa.org/record/2022-79821-001.

Parohan M, Yaghoubi S, Seraji A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality in patients with coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. Aging Male 2020;23(5):1416–24.

Ranjeva S, Pinciroli R, Hodell E, Mueller A, Hardin CC, Thompson BT, Berra L. Identifying clinical and biochemical phenotypes in acute respiratory distress syndrome secondary to coronavirus disease-2019. EClinicalMedicine 2021;34.

Sinha P, Furfaro D, Cummings MJ, Abrams D, Delucchi K, Maddali MV, He J, Thompson A, Murn M, Fountain J, Rosen A, Robbins-Juarez SY, Adan MA, Satish T, Madhavan M, Gupta A, Lyashchenko AK, Agerstrand C, Yip NH, Burkart KM, Beitler JR, Baldwin MR, Calfee CS, Brodie D, O'Donnell MR. Latent class analysis reveals COVID-19-related acute respiratory distress syndrome subgroups with differential responses to corticosteroids. Am J Respir Crit Care Med 2021;204(11):1274–85.

Su C, Xu Z, Hoffman K, Goyal P, Safford MM, Lee J, Alvarez-Mulett S, Gomez-Escobar L, Price DR, Harrington JS, Torres LK, Martinez FJ, Campion Jr TR, Wang F, Schenck EJ. Identifying organ dysfunction trajectory-based subphenotypes in critically ill patients with COVID-19. Sci Rep 2021;11(1):15872.

Tamuzi JL, Ayele BT, Shumba CS, Adetokunboh OO, Uwimana-Nicol J, Haile ZT, Inugu J, Nyasulu PS. Implications of COVID-19 in high burden countries for HIV/TB: a systematic review of evidence. BMC Infect Dis 2020;20(1):744.

Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18(5):1094–9.

Teng C, Thampy U, Bae JY, Cai P, Dixon RAF, Liu Q, Li P. Identification of phenotypes among COVID-19 patients in the United States using latent class analysis. Infect Drug Resist 2021;14:3865–71.

Wang C, Deng R, Gou L, et al. Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. Ann Transl Med 2020;8:593.

Wang X, Jehi L, Ji X, Mazzone PJ. Phenotypes and subphenotypes of patients with COVID-19: a latent class modeling analysis. Chest 2021;159(6):2191–204.

Webb BJ, Peltan ID, Jensen P, Hoda D, Hunter B, Silver A, Starr N, Buckel W, Grisel N, Hummel E, Snow G, Morris D, Stenehjem E, Srivastava R, Brown SM. Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study. Lancet Rheumatol 2020;2(12):e754–63.

WHO. Clinical management of COVID-19: interim guidance, May 27, 2020. https://apps.who.int/iris/bitstream/handle/10665/332196/WHO-2019-nCoV-clinical-2020.5-eng.pdf?sequence=1&isAllowed=y.

Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584(7821):430–6.

Yoo J, Grewal P, Hotelling J, Papamanoli A, Cao K, Dhaliwal S, Jacob R, Mojahedi A, Bloom ME, Marcos LA, Skopicki HA, Kalogeropoulos AP. Admission NT-proBNP and outcomes in patients without history of heart failure hospitalized with COVID-19. ESC Heart Fail 2021;8(5):4278–87.

Zemlin AE, Allwood B, Erasmus RT, Matsha TE, Chapanduka ZC, Jalavu TP, Ngah V, Sigwadhi LN, Koegelenberg CF, Irusen E, Lalla U, Yalew A, Baines N, Tamuzi JL, Barasa AK, Magutu VK, Njeru C, Amayo A, Mureithi MW, Mungania M, Sono-Setati M, Zumla A, Nyasulu PS. Prognostic value of biochemical parameters among severe COVID-19 patients admitted to an intensive care unit of a tertiary hospital in South Africa. IJID Reg 2022;2:191–7.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course, and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62.