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## Prognostic value of biochemical parameters among severe COVID-19 patients admitted to an intensive care unit of a tertiary hospital in South Africa

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### ABSTRACT

**Background:** Data on biochemical markers and their association with mortality rates in patients with severe coronavirus disease 2019 (COVID-19) admitted to intensive care units (ICUs) in sub-Saharan Africa are scarce. An evaluation of baseline routine biochemical parameters was performed in COVID-19 patients admitted to the ICU, in order to identify prognostic biomarkers.

**Methods:** Demographic, clinical, and laboratory data were collected prospectively from patients with PCR-confirmed COVID-19 admitted to the adult ICU of a tertiary hospital in Cape Town, South Africa, between October 2020 and February 2021. Robust Poisson regression methods and the receiver operating characteristic (ROC) curve were used to explore the association of biochemical parameters with severity and mortality.

**Abbreviations:** ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; AUC, area under the curve; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; hs-TnT, high-sensitivity troponin T; ICU, intensive care unit; IL, interleukin; KDIGO, Kidney Disease Improving Global Outcomes; IQR, interquartile range; K+, potassium; LDH, lactate dehydrogenase; Na+, sodium; NHLS, National Health Laboratory Service; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCR, polymerase chain reaction; PCT, procalcitonin; ROC, receiver operating characteristic; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TnT, troponin T.

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**Results:** A total of 82 patients (median age 53.8 years, interquartile range 46.4–59.7 years) were enrolled, of whom 55 (67%) were female and 27 (33%) were male. The median duration of ICU stay was 10 days (interquartile range 5–14 days); 54/82 patients died (66% case fatality rate). Baseline lactate dehydrogenase (LDH) (adjusted relative risk 1.002, 95% confidence interval 1.0004–1.004;  $P = 0.016$ ) and N-terminal pro B-type natriuretic peptide (NT-proBNP) (adjusted relative risk 1.0004, 95% confidence interval 1.0001–1.0007;  $P = 0.014$ ) were both found to be independent risk factors of a poor prognosis, with optimal cut-off values of 449.5 U/l (sensitivity 100%, specificity 43%) and 551 pg/ml (sensitivity 49%, specificity 86%), respectively.

**Conclusions:** LDH and NT-proBNP appear to be promising predictors of a poor prognosis in COVID-19 patients in the ICU. Studies with a larger sample size are required to confirm the validity of this combination of biomarkers.

## 1. Introduction

As of July 28, 2021, the coronavirus disease 2019 (COVID-19) pandemic had caused over 195 million infections and over 4.1 million deaths globally (Johns Hopkins University, 2021). South Africa was the worst affected country in Africa, with up to 2.3 million confirmed cases and 70 338 deaths (Johns Hopkins University, 2021). A range of COVID-19 manifestations have been observed, ranging from asymptomatic, to mild, moderate, severe, and fulminant (Wu et al., 2020). The more severe clinical presentations have been associated with a high viral load, increasing age, and the presence of comorbidities (Jin et al., 2020), resulting in higher risks of acute respiratory distress syndrome (ARDS), acute renal, hepatic, or cardiac injury, and death (Huang et al., 2020). Several reports from Asia, Europe, and the USA have indicated that deranged biochemical, inflammatory, and immunological parameters may be associated with a poor prognosis (Mehta et al., 2020; Thompson et al., 2020; Ferrari et al., 2020; Song et al., 2020; Karakoyun et al., 2021). Data on biochemical markers and the association with mortality observed in patients with severe COVID-19 disease admitted to intensive care units (ICUs) in sub-Saharan Africa are scarce.

The aim of this study was to evaluate baseline routine biochemical findings in patients admitted to the ICU of a tertiary hospital in the Western Cape of South Africa during the second wave and to correlate these to the severity of the disease.

## 2. Methods

### 2.1. Study population

This cohort study took place at Tygerberg Hospital, a 1380-bed tertiary hospital in Cape Town, South Africa. The hospital provides tertiary services to approximately 3.5 million people from the Western Cape Province.

The study population comprised 82 consecutive patients with a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR test, admitted to the adult ICU during the second wave between October 29, 2020 and February 10, 2021. The biochemical parameters assessed were those routinely collected in the ICU. Patients were triaged by the intensivists according to disease severity and the likely prognosis, in accordance with provincial guidelines (Critical Care Society of Southern Africa, 2020), and admission was dictated by bed availability.

### 2.2. Data collection

Due to the infection control risk, data were captured prospectively using photographs of written clinical notes at the bedside, which were securely stored electronically. The clinical data were entered remotely by a data-capturer into a Redcap database. The laboratory results were imported from the National Health Laboratory Service (NHLS) Laboratory Information System (TrakCare Lab Enterprise) into the database. Data were quality checked by the data entry supervisor to ensure that the data entered were of good quality and reliable.

### 2.3. Ethics

Patient confidentiality was ensured by labelling data with a unique episode number. The study was approved by the Health Research Ethics Committee of Stellenbosch University (approval number N20/04/002\_COVID-19). The research project was conducted according to the ethical principles of the Declaration of Helsinki.

### 2.4. Laboratory analyses

Serum samples were collected on ICU admission for all study participants. The samples were analysed in the NHLS Chemical Pathology Laboratory on a Roche cobas 6000 analyser (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's recommendations. The NHLS is the South African national state laboratory, providing laboratory services to over 80% of the population. The levels of the following parameters were determined: sodium ( $\text{Na}^+$ ) and potassium ( $\text{K}^+$ ) using indirect ion-selective electrode potentiometry, creatinine enzymatically, urea using a kinetic assay with urease, alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) enzymatically, bilirubin using the colorimetric diazo method, C-reactive protein (CRP) immunoturbidimetrically, high-sensitivity troponin T (hs-TnT), N-terminal pro-brain natriuretic peptide (NT-proBNP), procalcitonin (PCT), and ferritin using an electrochemiluminescent immunoassay, and glycated haemoglobin (HbA1c) using a turbidimetric inhibition immunoassay. The estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula without correction for race, a calculation recommended by the Kidney Disease Improving Global Outcomes (KDIGO) report (Levey et al., 2020). The NHLS Chemical Pathology Laboratory is accredited by the South African National Accreditation Services (SANAS), a regulatory body responsible for laboratory conformity to ISO15189 assessments in South Africa. Result quality is validated with internal quality control and the laboratory participates in an external quality control scheme.

### 2.5. Outcomes and predictor variables

The following data were collected: sociodemographic (age, sex), pre-existing comorbidities associated with severe COVID-19 outcome (hypertension, diabetes mellitus, and hyperlipidaemia), and routinely collected biochemistry. The primary outcome was the proportion of patients who died (non-survivors) after admission to the ICU. Time to death or discharge and length of stay in the ICU were assessed.

### 2.6. Statistical analysis

Continuous variables were expressed as the mean and standard deviation for normally distributed data and as the median with interquartile range (IQR) for non-normally distributed data. Categorical variables were expressed using frequencies and percentages. Robust Poisson regression was used to assess the significant association between demographic, laboratory results, and survival. Factors associated with death at a  $P$ -value  $< 0.15$  in the unadjusted univariable robust Poisson regression were included in a multivariable model to identify independent

factors associated with death. Due to the high prevalence of mortality, around 66%, the logistic regression overestimated the effect measure with large standard errors, resulting in wide confidence intervals; therefore robust Poisson regression was used. Adjusted incidence rate ratios and their 95% confidence intervals (CI) were used as a measure of association. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of various biochemical analytes to discriminate between patients with severe disease who survived and died. Factors with a  $P$ -value  $<0.05$  were considered significantly associated with mortality. All statistical analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA) and R version 4.0.2 (R Core Team) with R Studio version 1.3 (R Studio Team) statistical software.

### 3. Results

#### 3.1. Patient demographics

The study cohort comprised 82 patients with a median age of 53.8 years (IQR 46.4–59.7 years) who were admitted between October 2020 and February 2021. Table 1 shows the demographic characteristics of the study patients. There were 55 (67%) female patients and 27 (33%) male patients, and underlying comorbidities considered in this analysis were hypertension ( $n = 39$ , 57%), diabetes mellitus ( $n = 34$ , 50%), and hyperlipidaemia ( $n = 5$ , 7%).

The median duration of stay in the ICU was 10 days (IQR 5–14 days). Of the 82 patients with outcome data available at database closure, 54 (66%) died in the ICU. Table 1 provides descriptive data, showing that there was no statistically significant difference between survivors and non-survivors admitted to the ICU with regard to demographic characteristics, age, sex, and comorbidities.

#### 3.2. Baseline biochemical parameters

The comparison of baseline biochemical parameters in survivors and non-survivors is shown in Table 2. Electrolyte results, namely  $\text{Na}^+$  and  $\text{K}^+$ , showed no significant differences between the two groups ( $P = 0.37$  and  $P = 0.51$ , respectively). Regarding markers of renal function, there was no significant difference in urea or creatinine level between the two groups ( $P = 0.18$  and  $P = 0.097$ , respectively); however, the eGFR was decreased in the non-survivor group ( $P = 0.046$ ). There was no statistically significant difference in HbA1c between survivors and non-survivors ( $P = 0.33$ ).

With regard to markers of liver function, there was no significant difference in bilirubin or ALT between the two groups ( $P = 0.65$  and  $P = 0.81$ , respectively), but the non-specific marker LDH was significantly increased in non-survivors ( $P = 0.014$ ). Markers of cardiac function showed significantly increased levels of TnT and NT-proBNP in non-survivors ( $P = 0.006$  and  $P = 0.004$ , respectively). Markers of inflammation showed significantly higher levels of CRP and PCT in non-survivors ( $P = 0.014$  and  $P = 0.003$ , respectively). Although ferritin levels were increased, there was no statistically significant difference between survivors and non-survivors ( $P = 0.88$ ).

#### 3.3. Association of socio-demographic and biochemical parameters with survival

Table 3 shows the association between socio-demographic and biochemical parameters and survival in the study cohort. In the unadjusted univariate analysis, the relative risk (RR) was statistically significant for urea (1.03, 95% CI 1.01–1.06;  $P = 0.020$ ), creatinine (1.01, 95% CI 1.01–1.07;  $P = 0.003$ ), eGFR (0.99, 95% CI 0.98–0.99;  $P = 0.005$ ), LDH (1.01, 95% CI 1.01–1.04;  $P = 0.001$ ), TnT (1.02, 95% CI 1.01–1.03;  $P = 0.012$ ), NT-proBNP (1.01, 95% CI 1.01–1.03;  $P = 0.001$ ), CRP (1.02, 95% CI 1.03–1.04,  $P = 0.021$ ), and PCT (1.21, 95% CI 1.10–1.35;  $P <$

0.001). However, LDH and NT-proBNP also showed a significant association with a poor prognosis in the adjusted univariate analysis: adjusted RR 1.002 (95% CI 1.0004–1.004;  $P = 0.016$ ) and adjusted RR 1.0004 (95% CI 1.0001–1.0007;  $P = 0.014$ ), respectively.

#### 3.4. Cut-offs and ROC

As the adjusted RR was significant for LDH and NT-proBNP, the optimal cut-offs to predict non-survival were determined, and the performance of these two parameters was tested using ROC curves. The proposed optimum cut-off points that could predict COVID-19 severity and mortality in the ICU were  $\geq 449.5$  U/l for LDH (100% sensitivity, 43% specificity, area under the curve (AUC) 0.73) and  $\geq 551$  pg/ml for NT-proBNP (49% sensitivity, 86% specificity, AUC 0.72) (Table 4). However, the performance of both was suboptimal to allow the use of either one as a predictive marker on its own (see Figure 1).

### 4. Discussion

Although numerous studies globally have evaluated biochemical abnormalities in the first and second waves of COVID-19 (Mehta et al., 2020; Thompson et al., 2020; Ferrari et al., 2020; Song et al., 2020; Karakoyun et al., 2021), there is a paucity of data from Africa. South Africa experienced the second wave in late 2020 and this study examined patients admitted to the ICU during that period.

There were several notable findings from this study, including the observation that in non-survivors the eGFR was significantly decreased while the LDH levels were significantly increased. Furthermore, surrogate markers of cardiac dysfunction, namely TnT and NT-proBNP, and inflammatory markers, namely CRP and PCT, were significantly elevated among non-survivors. However, only LDH and NT-proBNP were significant predictors of disease severity.

Other biochemical parameters such as serum  $\text{Na}^+$  and  $\text{K}^+$  (Chen et al., 2020; Lippi et al., 2020a; Wang et al., 2020), CRP (Bonetti et al., 2020; Luo et al., 2020; Ponti et al., 2020; Tan et al., 2020; Yamada et al., 2020; Poggiali et al., 2020; Boufrioua et al., 2021), PCT (Ponti et al., 2020; Lippi and Plebani, 2020; Hesse et al., 2021), pro-inflammatory cytokines, albumin, and ferritin, which are biomarkers that have been linked with multi-organ failure among patients with severe COVID-19 admitted to the ICU (Mehta et al., 2020; Thompson et al., 2020; Zeng et al., 2020), were not significantly associated with COVID-19 after adjustment for confounders. However, several markers of organ dysfunction have been described as prognostic markers in COVID-19. These include markers of hepatocyte injury (bilirubin, ALT, and the non-specific enzyme, LDH) (Bonetti et al., 2020; Poggiali et al., 2020; Kermali et al., 2020), renal function (urea, creatinine, and eGFR) (Henry and Lippi, 2020), and cardiac function (hs-TnT and NT-proBNP) (Lippi et al., 2020b). Biochemical markers associated with severity include raised LDH, CRP, cardiac troponins, and NT-proBNP.

It appears that there is only one study from South Africa on biomarkers in the first wave. A study by Hesse et al. investigated laboratory findings of all patients with COVID-19 during a 4-month period (11.7% positive), and found that disease severity was associated with raised inflammatory markers, coagulation markers, liver, cardiac markers, and urea (Hesse et al., 2021). Two studies compared the first and second waves in South Africa. Jassat et al. only compared clinical outcomes and described more hospitalizations in patients who were older with fewer comorbidities and a 20% increased risk of in-hospital mortality (Jassat et al., 2021). Maslo et al. compared clinical and laboratory data in patients hospitalized in one hospital during both waves and found that patients admitted during the second wave were also older with fewer comorbidities and had significantly higher D-dimer and interleukin (IL)-6 levels (Maslo et al., 2021). As these findings are thought to be due to increased transmissibility of the variants of concern, other laboratory biomarkers may be useful to predict disease severity.

**Table 1**  
Demographic characteristics of COVID-19 patients admitted to the ICU

Characteristic	Total (%)	Survivors(n = 28)	Non-survivors(n = 54)	P-value
Age (years), median (IQR)	53.8 (46.4–59.7)	49.6 (42.0–60.2)	55.3 (47.2–58.1)	0.310
Sex				0.550
Female	55 (67%)	20 (71%)	35 (65%)	
Male	27 (33%)	8 (29%)	19 (35%)	
Smoker	13 (25%)	3 (17%)	10 (27%)	0.670
Duration of ICU stay	10 (5–14)	9.5 (5.5–14)	10 (5–13)	0.880
Hypertension	39 (57%)	12 (55%)	27 (59%)	0.750
Diabetes mellitus	34 (50%)	12 (55%)	22 (48%)	0.600
Hyperlipidaemia	5 (7%)	1 (5%)	4 (9%)	0.540

ICU, intensive care unit; IQR, interquartile range.

**Table 2**  
Baseline biochemical characteristics of COVID-19 patients admitted to the ICU

Analytes	Total	Reference intervals	TotalMedian (IQR)	Survivors(n = 28)Median (IQR)	Non-survivors(n = 54)Median (IQR)	P-value
Na <sup>+</sup>	82	135–145 mmol/l	137.5 (135–140)	137 (135–139.5)	138 (135–141)	0.370
K <sup>+</sup>	82	3.5–5.1 mmol/l	4.4 (3.8–4.7)	4.2 (3.8–4.7)	4.4 (3.9–4.7)	0.510
Urea	82	2.1–7.1 mmol/l	6.3 (4.9–8.3)	5.95 (4.4–7.9)	6.5 (5.1–8.8)	0.180
Creatinine	82	49–90 μmol/l	73.5 (64–98)	71 (63–78)	75.5 (66–107)	0.097
eGFR	82	>60 ml/min	83 (71–99)	88 (75.5–104.5)	80 (70–94)	0.046
HbA1c	77	<6.5%	7.6 (6.3–8.7)	7.8 (6.3–11.6)	7.5 (6.3–8.4)	0.330
Ca <sup>2+</sup>	58	2.12–2.59 mmol/l	2.07 (2.02–2.17)	2.1 (2.03–2.19)	2.06 (2.01–2.16)	0.450
Mg <sup>2+</sup>	53	0.63–1.05 mmol/l	0.94 (0.88–1.07)	0.89 (0.81–0.94)	0.98 (0.89–1.08)	0.019
Phosphate	53	0.78–1.42 mmol/l	1.15 (0.94–1.53)	1.16 (1.09–1.35)	1.14 (0.93–1.55)	0.940
TBil	73	5–21 μmol/l	7 (5–9)	7 (5–9)	7 (5–9)	0.650
ALT	74	<41 U/l	38.5 (23–50)	40 (23–65)	37 (22–49)	0.810
LDH	42	100–190 U/l	722 (579–900)	606 (346–846)	772 (633–957.5)	0.014
TnT	68	<100 ng/l	13.5 (6–28)	6 (5–16)	15 (9–37)	0.006
NT-proBNP	67	<125 pg/ml	220 (102–845)	116 (63–259)	309 (125–1390)	0.004
CRP	81	<10 mg/l	147 (96–221)	106.5 (69.5–186.5)	162 (110–235)	0.014
PCT	70	<0.5 ng/ml	0.36 (0.13–1.12)	0.16 (0.08–0.36)	0.57 (0.19–1.68)	0.003
Ferritin	61	13–150 μg/l	891 (440–1400)	937 (344–1400)	770 (440–1496)	0.880

ICU, intensive care unit; IQR, interquartile range; Na<sup>+</sup>, sodium; K<sup>+</sup>, potassium; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; Ca<sup>2+</sup>, calcium; Mg<sup>2+</sup>, magnesium; TBil, total bilirubin; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; TnT, troponin T; NT-proBNP, N-terminal B-type natriuretic peptide; CRP, C-reactive protein; PCT, procalcitonin.

**Table 3**  
Association of socio-demographic and biochemical parameters with mortality status among patients admitted to the COVID-19 ICU

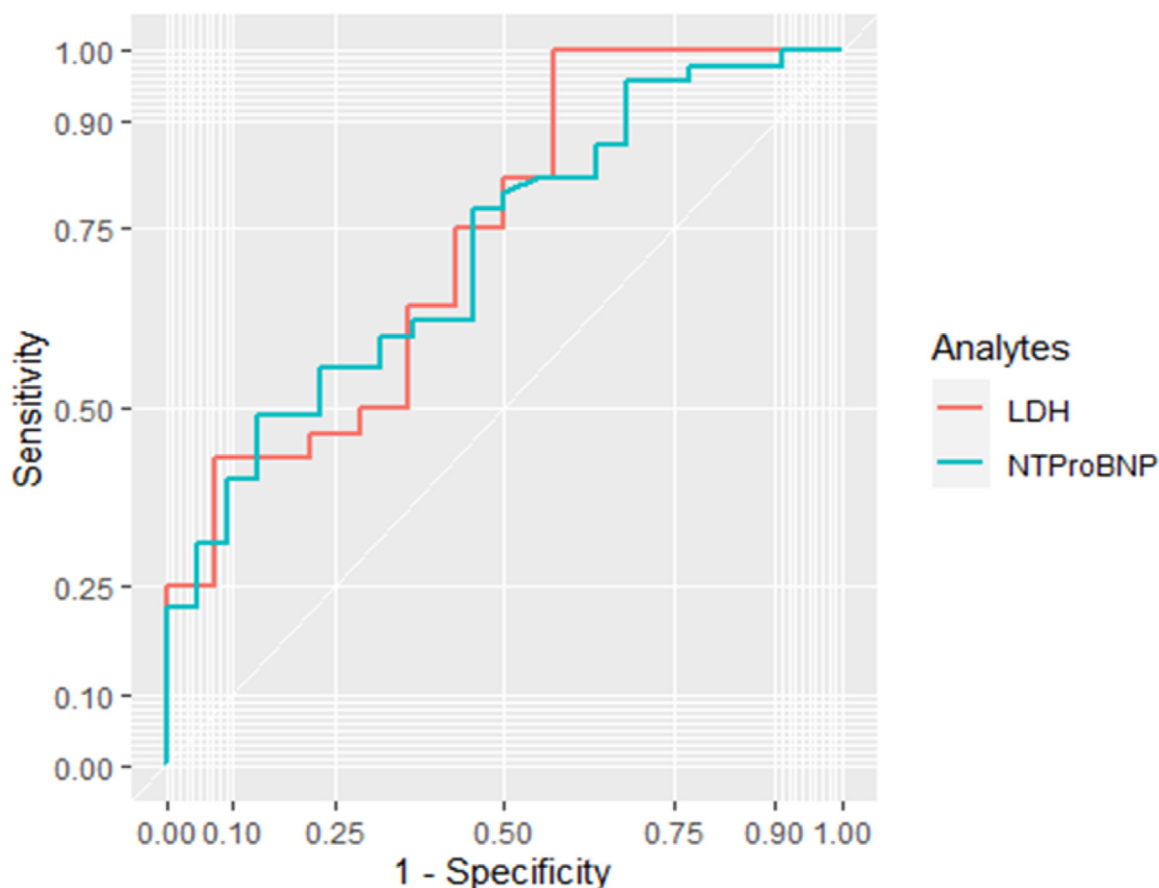
Characteristic	Unadjusted RR(95% CI)	P-value	Adjusted RR(95% CI)	P-value
Age	1.00 (0.99–1.03)	0.308		
Sex: Male	1.19 (0.86–1.64)	0.298		
Duration of ICU stay	0.99 (0.97–1.01)	0.424		
Hypertension	1.06 (0.75–1.48)	0.753		
Asthma	0.73 (0.18–2.99)	0.665		
Diabetes mellitus	0.92 (0.66–1.28)	0.608		
Hyperlipidaemia	1.20 (0.75–1.93)	0.452		
Na <sup>+</sup>	1.01 (0.97–1.04)	0.722		
K <sup>+</sup>	1.10 (0.90–1.35)	0.370		
Urea	1.03 (1.01–1.06)	0.020	0.86 (0.74–1.01)	0.073
Creatinine	1.01 (1.01–1.07)	0.003	0.99 (0.98–1.01)	0.530
eGFR	0.99 (0.98–0.99)	0.005	0.99 (0.97–1.01)	0.453
HbA1c	0.95 (0.87–1.03)	0.206		
Ca <sup>2+</sup>	0.95 (0.27–3.39)	0.941		
Mg <sup>2+</sup>	1.02 (0.44–2.39)	0.956		
Phosphate	1.13 (0.95–1.35)	0.172		
TBil	1.01 (1.00–1.03)	0.667		
ALT	1.00 (0.99–1.00)	0.631		
LDH	1.01 (1.01–1.04)	0.001	1.002 (1.0004–1.004)	0.016
TnT	1.02 (1.01–1.03)	0.012	0.99 (0.98–1.004)	0.199
NT-proBNP	1.01 (1.01–1.03)	0.001	1.0004 (1.0001–1.0007)	0.014
CRP	1.02 (1.03–1.04)	0.021	1.001 (0.999–1.003)	0.251
PCT	1.21 (1.10–1.35)	<0.001	1.14 (0.96–1.36)	0.135
Ferritin	1.00 (0.99–1.00)	0.893		

ICU, intensive care unit; RR, relative risk; CI, confidence interval; Na<sup>+</sup>, sodium; K<sup>+</sup>, potassium; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; Ca<sup>2+</sup>, calcium; Mg<sup>2+</sup>, magnesium; TBil, total bilirubin; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; TnT, troponin T; NT-proBNP, N-terminal B-type natriuretic peptide; CRP, C-reactive protein; PCT, procalcitonin.

**Table 4**  
Optimal cut-off, sensitivity, specificity, and AUC for LDH and NT-proBNP

Analyte	Direction	Optimal cut-off point	Sensitivity	Specificity	AUC
LDH	≥	449.5 U/L	1	0.43	0.73
NT-proBNP	≥	551 pg/mL	0.49	0.86	0.72

AUC, area under the receiver operating characteristic curve; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro B-type natriuretic peptide.



**Figure 1.** ROC curve of the predictor effect of combined LDH (lactate dehydrogenase) and NT-proBNP (N-terminal pro B-type natriuretic peptide) for a poor prognosis.

In the present study cohort, routine biochemical tests were examined, which included electrolytes, markers of renal, hepatic, and cardiac dysfunction, and markers of inflammation, and these were correlated with survival.

As hepatocytes express angiotensin-converting enzyme 2 (ACE2) receptors, liver damage may be due to direct infection (Chai et al., 2020), but also to hepatotoxic drugs, the systemic inflammatory response, hypoxia, or multi-organ failure (Feng et al., 2020). In the present study cohort, no significant difference in bilirubin or ALT levels was found; however, LDH was significantly raised in non-survivors. This is in agreement with the results of previous studies, and high LDH was one of the first markers of disease severity described (Poggiali et al., 2020; Kermali et al., 2020; Ferrari et al., 2020). LDH is not liver-specific and this increase in LDH is thought to be due to lung damage induced by SARS-CoV-2 (Han et al., 2020). It must be noted that even though levels were significantly higher in the non-survivors in the study cohort, both groups had levels well above the higher reference limit, in concordance with the observation by Kermali et al. (Kermali et al., 2020).

The risk of cardiac dysfunction is increased in COVID-19 and possible causes include direct cytopathic injury due to the presence of ACE2

receptors on cardiac myocytes, cytokine-mediated damage, ischaemia, or exacerbation of pre-existing cardiac disease (Akhmerov and Marbán, 2020; Khan et al., 2020). Like previous studies, significantly higher TnT and NT-proBNP levels were found in non-survivors (Lippi et al., 2020b; Gao et al., 2020). The American College of Cardiology stated that increased TnT and NT-proBNP levels do not necessarily suggest acute coronary syndrome and must be interpreted in the correct clinical context, taking the clinical picture of the patient into consideration (American College of Cardiology, 2020).

The cytokine storm in COVID-19 is associated with worse outcomes and increased levels of pro-inflammatory cytokines such as IL-6 (Mehta et al., 2020; Song et al., 2020). This affects acute phase reactants, leading to increased CRP and ferritin and decreased albumin levels (Mehta et al., 2020). Most laboratories, including the NHLS Chemical Pathology Laboratory, do not routinely analyse IL-6. However, CRP is synthesized in the liver under the influence of IL-6 and therefore reflects IL-6 levels (Boras et al., 2014; Sproston and Ashworth, 2018). Significantly increased CRP levels were found in non-survivors, which is in agreement with the published literature (Bonetti et al., 2020; Luo et al., 2020; Ponti et al., 2020; Tan et al., 2020; Yamada et al.,

2020; Poggiali et al., 2020; Boufrioua et al., 2021). Unfortunately, albumin was not measured routinely in the study patients and therefore numbers were too few to analyse.

PCT is normally produced in the C-cells of the thyroid and levels are undetectable in health. However, during infection (especially bacterial), levels rise due to extra-thyroidal synthesis (Karzai et al., 1997). Increased PCT levels were found in non-survivors in the present study, which is also consistent with other studies (Ponti et al., 2020; Lippi and Plebani, 2020; Hesse et al., 2021). Although previous studies have found increased ferritin (Cheng et al., 2020) or no difference in ferritin levels (Wu et al., 2020) between COVID-19 survivors and non-survivors, this study found increased levels in survivors. However, this difference was not statistically significant and the numbers were small.

When analysing the unadjusted RR in the study cohort, urea, creatinine, eGFR, LDH, TnT, NT-proBNP, CRP, and PCT were significantly associated with the risk of non-survival. However, regarding the adjusted RR, only LDH and NT-proBNP were significantly associated with increased risk. The optimal cut-off values of these two analytes to predict severity were then determined. However, the performance of both was suboptimal to allow for the use of either one as a predictive marker on its own.

Chronic kidney disease is associated with worse outcomes in COVID-19 (Henry and Lippi, 2020). In this study, slightly higher urea and creatinine with lower eGFR levels were found in non-survivors, but these differences were neither statistically nor clinically significant. Other studies have reported higher urea levels to be associated with severity (Bonetti et al., 2020; Boufrioua et al., 2021).

No significant difference in Na<sup>+</sup> or K<sup>+</sup> levels was found between survivors and non-survivors. Few studies have evaluated electrolyte disturbances in COVID-19 (Chen et al., 2020; Lippi et al., 2020a; Wang et al., 2020) and many have reported hypokalaemia to be associated with worse outcomes and exacerbation of ARDS and cardiac injury. As the SARS-CoV-2 virus enters the cells using the ACE2 receptor and thereby influences the renin-angiotensin system, renal loss of K<sup>+</sup> is thought to be the cause of electrolyte disorders in these patients (Chen et al., 2020; Lippi et al., 2020a). Electrolytes may be also influenced by other clinical manifestations of these patients, such as gastrointestinal loss due to diarrhoea and vomiting and multi-organ failure (Chen et al., 2020).

The study also found that non-survivors were slightly older and more likely to be smokers, and that the proportion of male patients who died was slightly higher than the proportion of female patients who died, although none of these results were statistically significant. Comorbidities such as hypertension and diabetes mellitus have been shown to be predictors of non-survival (Savoia et al., 2021; Prattichizzo et al., 2021). The association of hypertension with a severe outcome has been postulated to be because of the action of SARS-CoV-2 on the renin-angiotensin system (Savoia et al., 2021). Diabetes mellitus with high HbA1c is associated with worse SARS-CoV-2 outcomes (Prattichizzo et al., 2021). However, in the current study cohort, although 57% of the participants were hypertensive, no significant difference in the frequency of hypertension or diabetes mellitus was found between survivors and non-survivors.

It must however be noted that the median HbA1c levels were raised at >7% in both groups. A level of >6.5% is diagnostic of diabetes. The study results agree with those of a recent study conducted in South Africa (Hesse et al., 2021).

This study has some limitations. The population was small and only baseline ICU admission laboratory data were analysed. A larger sample population may have increased the statistical significance of the markers. Ideally, an analysis of the trend over their ICU stay would have been performed, but the numbers were too small on subsequent days. This study also has certain strengths, namely, all patients were admitted to the same ICU and had samples analysed on admission in the same laboratory, ensuring harmonization of the pre-analytical and analytical phases of testing. Further larger studies are needed to evaluate these biomarkers to determine their use in developing a risk score, as earlier identification of patients at high risk of a poor prognosis and the in-

stitution of early interventions may be effective in reducing COVID-19 mortality among patients admitted to the ICU.

In conclusion, this study identified LDH and NT-proBNP as biochemical markers possibly associated with poor COVID-19 outcomes in patients admitted to the ICU. To increase the predictive probability, there is a need to combine biomarker assessments and not only rely on a single parameter estimate; for example combining LDH and NT-proBNP increases the sensitivity of predicting mortality rather than relying on a single biomarker.

#### Declaration of Competing Interest

No conflict of interest declared.

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#### Author contributions

All authors contributed to the ideation, the collection, analyses, and interpretation of the data, and writing of the manuscript.

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#### Informed consent statement

The investigators obtained ethical approval and a waiver of consent from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University, and the Research Ethics Committee of Tygerberg Hospital (approval number N20/04/002\_COVID-19).

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