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Predicting COVID-19 outcomes from clinical and laboratory parameters in an intensive care facility during the second wave of the pandemic in South Africa

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ABSTRACT

Background: The second wave of coronavirus disease 2019 (COVID-19) in South Africa was caused by the Beta variant of severe acute respiratory syndrome coronavirurus-2. This study aimed to explore clinical and biochemical parameters that could predict outcome in patients with COVID-19.

Methods: A prospective study was conducted between 5 November 2020 and 30 April 2021 among patients with confirmed COVID-19 admitted to the intensive care unit (ICU) of a tertiary hospital. The Cox proportional hazards model in Stata 16 was used to assess risk factors associated with survival or death. Factors with $P<0.05$ were considered significant.

Results: Patients who died were found to have significantly lower median pH ($P<0.001$), higher median arterial partial pressure of carbon dioxide ($P<0.001$), higher D-dimer levels ($P=0.001$), higher troponin T levels (P=0.001), higher N-terminal-prohormone B-type natriuretic peptide levels ($P=0.007$) and higher C-reactive protein levels ($P=0.010$) compared with patients who survived. Increased standard bicarbonate (HCO3std) was associated with lower risk of death (hazard ratio 0.96, 95% confidence interval 0.93–0.99).

Conclusions: The mortality of patients with COVID-19 admitted to the ICU was associated with elevated D-dimer and a low HCO3std level. Large studies are warranted to increase the identification of patients at risk of poor prognosis, and to improve the clinical approach.

Introduction

There have been >472 million cases of coronavirus disease 2019 (COVID-19) and >6 million deaths worldwide as of 24 March 2022 (World Health Organization, 2022). Due to the continuous transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) around the world, mutations of the virus led to waves of COVID-19 (Fontanet et al., 2021; Mascola et al., 2021; Zhang et al., 2021). One of these mutations was designated as the 'Beta variant'. This was

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reported to be more transmissible than the original (Alpha) strain of SARS-CoV-2, and there were concerns that the Beta strain would be resistant to the vaccine which was developed based on the original strain (Mascola et al., 2021; Tegally et al., 2021). The Beta variant was first reported in the Eastern Cape province of South Africa in October 2020 (Tegally et al., 2021), and spread globally (Tang et al., 2021a, b).

A study of the second wave of COVID-19 in Vietnam found that fewer older people (mean age 46 years) and more females were infected compared with the first wave (Nong et al., 2021). Comparative studies found differences in mortality between the first two waves. While some studies showed that the second wave had more incident cases than the first wave, including static numbers of intensive care unit (ICU) admissions and deaths (Coccia, 2021; Salyer et al., 2021), other studies showed a reduction in mortality during the second wave (Fan et al., 2021; James et al., 2021; Nong et al., 2021).

In Africa, as of 31 December 2020, 40 countries were already experiencing their second wave, with the continent reporting a mean of 23,790 new cases each day for epidemiological week 53 (Salyer et al., 2021). South Africa was the most severely affected country in Africa, with >80,000 deaths by the end of December 2020, with the second wave starting in October 2020 (Frean, 2021). The Western Cape, Eastern Cape and KwaZulu–Natal provinces were most affected by the second wave, with the Western Cape province reaching a peak infection level higher than that of the first wave (Frean, 2021; Tegally et al., 2021). Analysis of data from the national active surveillance system for COVID-19 hospitalizations showed that individuals hospitalized in the second wave were more likely to be older (>40 years) and less likely to have comorbidities compared with the first wave (Jassat et al., 2021). This study also found a higher incidence of positive cases, increased number of hospitalizations, and increased in-hospital mortality in the second wave compared with the first wave (Jassat et al., 2021). Identification of specific clinical and laboratory biomarkers indicating high risk of mortality may improve decision-making for COVID-19 management in clinical practice. As such, this prospective study was conducted between 5 November 2020 and 30 April 2021 to define clinical features and laboratory biomarkers associated with increased risk of mortality in patients with COVID-19 admitted to the ICU at a tertiary hospital in the Western Cape province during the second wave of COVID-19 in South Africa.

Methods

Study population

This study was conducted at Tygerberg Hospital, a 1380-bed tertiary hospital in Cape Town. The hospital provides tertiary services to approximately 3.5 million people in the Western Cape province. Many people serviced by the hospital are from low-income areas, with a significant proportion living in low-cost and informal settlements where overcrowding, shared ablution and water facilities make social distancing and the advocated hygiene methods difficult. The study population comprised all consecutive patients admitted to the adult ICU between 5 November 2020 and 30 April 2021, when the database was censored. Over the course of the pandemic, the capacity of the ICU fluctuated. According to provincial guidelines, patients referred to the ICU were triaged by the consultants on duty based on disease severity and likely prognosis, and admissions were contingent on bed availability (Critical Care Society of Southern Africa, 2021).

Data collection

Data were captured prospectively each day using photographs of bedside clinical notes, which were securely stored electronically. Clinical data were entered remotely by a data-capturer into the Redcap database, and laboratory results were imported from the National Health Laboratory Services into the database. Data were quality checked by the data entry supervisor to ensure that the information entered was of high quality and reliable.

Outcome and predictor variables

Data collected included sociodemographic details (age, sex, socioeconomic status), clinical disease characteristics, pre-existing comorbidities [hypertension, diabetes, cardiovascular disease, chronic lung disease, obesity, and human immunodeficiency virus (HIV)], routinely collected laboratory data, mode of respiratory support, and clinical management strategy. The primary outcome of interest was the proportion of patients who died after admission to the ICU, including those who were discharged from the ICU and died in hospital. Time to death or censored (alive at discharge) was also assessed.

Statistical analysis

Continuous variables have been expressed as median and interquartile range (IQR) for skewed data. Categorical variables have been expressed as frequency and percentage. A multi-variable model was developed for demographics, comorbidities, drugs, clinical symptoms and biochemical parameters using variables strongly associated with mortality or survival outcomes on univariate analysis. For comparison between mortality and survival, Pearson's Chi-squared test or Fisher's exact test were used, where appropriate, for categorical variables, and Wilcoxon's rank-sum test was used for continuous variables. Factors associated with death or survival with a P-value <0.05 on unadjusted univariate analysis were considered to be significant. The log-rank test and the Wilcoxon test were used to compare the survival functions for each sociodemographic, clinical and biochemical covariate. Hazard ratios (HRs) were calculated using Cox's proportional hazards model to assess the risk factors associated with survival and death. All statistical analyses were performed using Stata Version 16 (Stata Corp, College Station, TX, USA).

Results

In this cohort, 82 patients were admitted to the ICU from 5 November to 30 April 2021. Among them, 27 (33%) were males. Table 1 shows the characteristics of patients who died or survived while admitted to the ICU. The median age of patients who survived was not significantly different from that of patients who died: 50.4 (IQR 39.9–60.5) vs 55.2 (IQR 47.2–58.1) (P=0.497). Underlying comorbidities were hypertension (48%), diabetes mellitus (41%), HIV (11%), hyperlipidaemia (6%) and asthma (2%) (Table 1).

Median length of stay in the ICU was 12 (IQR 8–17) days. The most common clinical features at presentation were fever (30%) and myalgia (29%) (Table 1).

Median pH was 0.07 lower among patients who died compared with those who survived (P<0.001), whereas median $PaCO_2$ was 0.95 kPa higher among those who died (P<0.001) (Table 1). The D-dimer level was higher among patients who died compared with those who survived [1.51 (IQR 0.65–4.86) vs 0.41 (IQR 0.24–0.95); P<0.001) (Table 1). Finally, baseline levels of biochemical parameters, namely median troponin T (TropT), N-terminal pro B-type natriuretic peptide (NT-proBNP) and C-reactive protein (CRP), were significantly higher among patients who died compared with those who survived: median 18 vs 6 (P=0.001), 254.50 vs 110 (P=0.007), and 167.50 vs 106.00 (P=0.010), respectively (Table 1).

The multi-variate Cox proportional hazards model was used to assess the relationship between various covariates and patient survival or risk of death. The data show that an elevated D-dimer level was associated with increased risk of death in the ICU [HR 1.05, 95% confidence interval (CI) 1.00–1.11], and an elevated standard bicarbonate (HCO3std) level was associated with a reduced risk of death (HR 0.96, 95% CI 0.93–0.99). Furthermore, an increased lymphocyte count was associated with a higher probability of survival (HR 1.10, 95% CI 1.02–1.19). (Table 2).

Table 1
Comparison of patient characteristics between those who died and those who survived.

Factor	Level	*n*	Total (*n*=82)	Discharge (*n*=28)	Death (*n*=54)	*P*-value
Age at diagnosis (years)		75		50.41 (39.89–60.54)	55.22 (47.20–58.07)	0.497
Gender	Female	82	55 (67%)	20 (71%)	35 (65%)	0.546
	Male		27 (33%)	8 (29%)	19 (35%)	
Smoking Status	Non-smoker	82	41 (50%)	15 (54%)	26 (48%)	0.420
	Former smoker		10 (12%)	3 (11%)	7 (13%)	
	Current smoker		3 (4%)	0 (0%)	3 (6%)	
	Unknown		28 (34%)	10 (36%)	18 (33%)	
Septic shock	No	82	57 (70%)	17 (61%)	40 (74%)	0.360
	Yes		2 (2%)	0 (0%)	2 (4%)	
	Unknown		23 (28%)	11 (39%)	12 (22%)	
Fever	No	82	35 (43%)	14 (50%)	21 (39%)	0.999
	Yes		25 (30%)	5 (18%)	20 (37%)	
	Unknown		22 (27%)	9 (32%)	13 (24%)	
Myalgia	No	82	35 (43%)	14 (50%)	21 (39%)	0.122
	Yes		24 (29%)	5 (18%)	19 (35%)	
	Unknown		23 (28%)	9 (32%)	14 (26%)	
Nausea	No	82	57 (70%)	17 (61%)	40 (74%)	0.058
	Yes		2 (2%)	0 (%)	2 (4%)	
	Unknown		23 (28)	11 (39%)	12 (28%)	
Antibiotics	No		66 (80%)	25 (89%)	41 (76%)	0.190
	Yes		15 (18%)	3 (11%)	12 (22%)	
	Unknown		1 (1%)	0 (0%)	1 (2%)	
Acute kidney injury	No		49 (60%)	17 (61%)	32 (59%)	0.227
	Yes		12 (15%)	2 (7%)	10 (19%)	
	Unknown	82	21 (26%)	10 (36%)	19 (35%)	
Hypertension	No		29 (35%)	12 (43%)	27 (50%)	0.746
	Yes		39 (48%)	6 (21%)	8 (15%)	
	Unknown		14 (17%)			
Asthma	No	82	66 (80%)	21 (75%)	45 (83%)	0.546
	Yes		2 (2%)	1 (4%)	1 (2%)	
	Unknown		14 (17%)	6 (21%)	8 (15%)	
Diabetes mellitus	No	82	34 (41%)	10 (36%)	24 (44%)	0.604
	Yes		34 (41%)	12 (43%)	22 (41%)	
	Unknown		14 (17%)	6 (21%)	8 (15%)	
Hyperlipidaemia	No	82	63 (77%)	21 (75%)	42 (78%)	0.999
	Yes		5 (6%)	1 (4%)	4 (7%)	
	Unknown		14 (17%)	6 (21%)	8 (15%)	
HIV status	Negative	82	66 (80%)	26 (93%)	40 (74%)	0.470
	Positive		9 (11%)	2 (7%)	7 (13%)	
	Unknown		7 (9%)	0 (0%)	7 (13%)	
Anticoagulants	No	82	11 (13%)	2 (7%)	9 (17%)	0.314
	Yes		70 (85%)	26 (93%)	44 (81%)	
	Unknown		1 (1%)	0 (0%)	1 (2%)	
Corticosteroids	No	82	15 (18%)	4 (14%)	11 (20%)	0.560
	Yes		66 (80%)	24 (86%)	42 (78%)	
	Unknown		1 (1%)	0 (0%)	1 (2%)	
pH, median (IQR)		82	7.45 (7.39–7.49)	7.48 (7.46–7.50)	7.41 (7.31–7.46)	<0.001
$paCO_2$ (kpa), median (IQR)		82	5.5 (4.9–6.3)	5.05 (4.80–5.30)	6.00 (5.20–6.90)	<0.001
paO_2 (kpa), median (IQR)		82	8 (6.8–8.8)	8.05 (6.80–8.70)	7.95 (6.80–9.00)	0.950
$K^{+,}$ median (IQR)		82	4.3 (3.8–4.7)	4.15 (3.80–4.65)	4.40 (3.90–4.70)	0.305
Lactate, median (IQR)		82	1.6 (1.2–2.3)	1.40 (1.05–1.95)	1.65 (1.40–2.40)	0.074
HCO3std, median (IQR)		74	28.25 (26.40–30.20)	28.20 (27.13–29.30)	28.40 (24.80–30.50)	0.937
SO2 (a), median (IQR)		82	91 (88–93)	92.50 (89.70–94.20)	90.20 (86.20–93.00)	0.084
PF Ratio, median (IQR)		82	72.68 (56.25–96.00)	84.22 (61.41–113.25)	68.39 (54.00–87.21)	0.052
Length of stay in hospital, median (IQR)		82	12 (8–17)	15.00 (9.50–20.00)	11.00 (7.00–16.00)	0.009
Temperature, median (IQR)		82	37.1 (36.7–37.8)	37.20 (36.80–38.10)	37.10 (36.70–37.80)	0.91
D-dimer, median (IQR)		82	1.03 (0.41–3.91)	0.41 (0.24–0.95)	1.51 (0.65–4.86)	<0.001
HbA1c, median (IQR)		72	7.6 (6.3–8.8)	7.80 (6.30–11.60)	7.50 (6.30–8.60)	0.348
Platelets, median (IQR)		76	309 (240–383)	321.50 (250.00–412.50)	275.00 (240.00–366.50)	0.277
TropT, median (IQR)		58	13 (6–27)	6.00 (4.00–15.00)	18.00 (9.00–40.00)	0.001
NT-proBNP, median (IQR)		54	178.5 (89–791)	110.00 (43.00–230.00)	254.50 (119.00–1467.00)	0.007
CRP, median (IQR)		73	148.00 (89.00–224.00)	106.00 (67.00–198.00)	167.50 (120.00–237.00)	0.010

BMI, body mass index; HIV, human immunodeficiency virus; HbA1c, haemoglobin A1C; K^+, potassium; NT-proBNP, N-terminal pro B-type natriuretic peptide; CRP, C-reactive protein; $paCO_2$, partial pressure of carbon dioxide; pH, potential hydrogen; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; TropT, troponin T; HCO_3std, standard bicarbonate is PF ratio, arterial partial pressure of oxygen (in mmHg)/inspired oxygen concentration; sO_2(a), oxygen saturation of arterial blood.
P-values computed computed based on the assumption that the null hypothesis is true .
For smoking status, former and current smokers considered as one group.

Table 2
Comparison of Cox proportional hazards ratio in relation to risk of discharge and death.

Discharge					Death			
	PHR	SD	2.5	97.5	PHR	SD	2.50	97.50
Age category (years)								
<50	Reference							
50–59	0.73	2.22	0.15	3.49	0.97	1.62	0.37	2.46
≥60	0.62	1.95	0.16	2.21	0.96	1.53	0.42	2.22
HIV								
Negative	Reference							
Positive	0.94	2.54	0.13	5.11	1.72	1.66	0.61	4.48
Hypertension								
No								
Yes	0.80	2.07	0.19	3.20	1.07	1.54	0.46	2.46
Gender								
Male	Reference							
Female	1.98	2.05	0.46	7.81	1.65	1.50	0.74	3.62
Hyperlipidaemia								
No								
Yes	1.02	3.74	0.06	10.31	1.19	1.96	0.30	4.13
Diabetes mellitus								
No								
Yes	1.51	2.09	0.33	6.03	0.73	1.56	0.30	1.72
Asthma								
No								
Yes	4.11	3.54	0.27	38.92	2.30	3.02	0.20	15.32
Continuous variables								
PF ratio	1.00	1.00	0.99	1.01	1.00	1.00	0.99	1.00
SO_2(a)	1.02	1.04	0.96	1.12	0.98	1.01	0.96	1.00
PTT ratio	2.10	1.53	0.89	4.73	0.92	1.39	0.47	1.71
D-dimer	0.86	1.09	0.71	0.99*	1.05	1.03	1.00	1.11*
TropT	0.96	1.03	0.90	1.01	1.00	1.00	1.00	1.01
Lymphocytes	1.10	1.04	1.02	1.19*	0.98	1.03	0.93	1.03
BMI	0.53	1.69	0.18	1.45	0.66	1.43	0.33	1.34
Platelets	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
HCO3std	0.96	1.04	0.90	1.03	0.96	1.02	0.93	0.99*
HbA1c	1.01	1.09	0.85	1.19	1.08	1.06	0.96	1.21

BMI, body mass index; HbA1c, haemoglobin A1C; HIV, human immunodeficiency virus; NT-proBNP, N-terminal pro B-type natriuretic peptide; CRP, C-reactive protein; $paCO_2$, partial pressure of carbon dioxide; pH, potential hydrogen; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; SaO_2, arterial oxygen saturation; PTT: partial thromboplastin time; SD, standard deviation; TnT, troponin T; HCO3std, standard bicarbonate; P/F ratio, arterial partial pressure of oxygen (in mmHg)/inspired oxygen concentration; PHR, posterior hazard ratio; sO_2(a), oxygen saturation of arterial blood.

Discussion

This study, conducted during the second wave of COVID-19 in South Africa, found that, among patients with COVID-19 admitted to the ICU, those who died had significantly higher D-dimer, TropT, NT-proBNP, CRP and $PaCO_2$ levels and significantly lower pH compared with those who survived, however on multivariate Cox's proportional hazards regression model, only a higher HCO3, and lower D-Dimer were significantly associated with outcome. In contrast, there were no significant differences in any of the clinical features or co-morbidities between those that survived or died.

Hypertension and diabetes were the most common co-morbidities, the observed increased HCO3 level among COVID-19 patients requires further investigation (Elezagic et al., 2021). In critically ill COVID-19 patients, acidosis has been viewed to be multifactorial and may be caused by hypercapnia and multiorgan failure (Bezuidenhout et al., 2021; Elezagic et al., 2021). Thus the association of lower pH level with lower patient survival rates is perhaps unsurprising (Bezuidenhout et al., 2021; Elezagic et al., 2021; Skevaki et al., 2020). However, the mean pH of 7.41 among patients who died could be considered relatively normal on admission (normal range: 7.35-7.45), by contrast the patients discharged alive were by comparison significantly more alkalotic on admission (pH of 7.48). The reason for this is unclear. Although the P/F ratio was higher in the surviving group, it would still be considered severely reduced, and the pH would not be clinically suspected to be abnormally raised. One hypothesis is that SARS-CoV-2 has a direct viral effect on the renin angiotensin aldosterone system leading to a metabolic alkalosis (Wiese et al., 2020).

D-dimer is another important biomarker being studied as a potential prognostic factor of disease severity in patients with COVID-19 (Zheng et al., 2020; Zhao et al., 2021). An elevated D-dimer level indicates activation of the fibrinolytic system, and the removal of clots or extravascular fibrin collection by plasmin (Zhao et al., 2021). In patients with COVID-19, an increase in the D-dimer level could be the result of increased inflammation, a sign of thromboembolism, or a potentially fatal consequence of hypercoagulation and fibrinolytic abnormalities (Zhao et al., 2021). In critically ill patients with COVID-19, pulmonary embolism can additionally cause respiratory failure (Chan et al., 2020; Cobre et al., 2021; Connors and Levy, 2020; Della Bona et al., 2021; Helms et al., 2020; Ly et al., 2020; Zhao et al., 2021).

The positive relationship between the D-dimer level and the percentage of male patients in COVID-19 studies suggests that men are more severely affected than women when admitted to the ICU (Zhao et al., 2021). In contrast, in the present study, more women than men were admitted to the ICU during the second wave. This could be explained by pre-existing medical conditions which are more common in women, such as hypertension, diabetes and asthma, all of which are associated with D-dimer level (Statsenko et al., 2021). Furthermore, four systemic complications – sepsis, secondary infection, disseminated intravascular coagulation and coagulopathy – were found to be significantly associated with D-dimer level (Ji et al., 2020). Comparison of survival rates by biochemical covariate showed that a lower D-dimer level was associated with a lower risk of mortality.

An elevated cardiac TropT level has high specificity for cardiac injury, and is a preferred biomarker for cardiac injury. A systematic review of eight studies, including a total of 1028 patients with COVID-

19, found increased risk of severe COVID-19 in patients with elevated TropT levels admitted to the ICU [relative risk (RR) 15.10, 95% CI 4.10–55.61; $P<0.001$], and the proportions of patients with elevated TropT levels were 14.3% and 63.9% in survivors and non-survivors, respectively, showing that a higher proportion of non-survivors had elevated TropT levels (RR 4.69, 95% CI 3.39–6.48, $P<0.001$) (Li et al., 2020). The present results showed that Trop T was higher in patient that died on univariate analysis, however, the results of the multivariate analysis suggest that although technically significant, this difference is marginal at best, likely reflecting a small sample size, and require further investigation with a larger sdample before definitive conclusions can be made.

Increased BNP and NT-proBNP secretion from the heart in response to high ventricular filling pressures is routinely used as a diagnostic and prognostic marker for heart failure, and is sometimes used as a marker for the size or severity of ischaemic insults (Omland et al., 2002; Maisel et al., 2018; Potter et al., 2009; Zinellu et al., 2021). A recent systematic review of 44 studies, with a total of 18,856 patients with COVID-19, found a significant association between plasma BNP/NT-proBNP levels, disease severity and mortality in these patients, which likely reflects the presence of cardiac involvement and its adverse sequelae in this group (Zinellu et al., 2021). Several studies have suggested that an increased serum CRP level is a reliable indicator of the presence and severity of SARS-CoV-2 infection (Kermali et al., 2020; Liu et al., 2020; Wang, 2020). A recent systematic review of eight studies, with a total of 2107 participants, found moderate certainty that a high blood CRP level provides valuable prognostic information on mortality and/or severe disease in patients with COVID-19 (Izcovich et al., 2020). The same study showed that mortality increased by 13.2% in patients with severe COVID-19 with elevated CRP levels (Izcovich et al., 2020). In contrast, a meta-analysis of 13 studies found that an elevated CRP level was associated with severe COVID-19 and the need for ICU care, but not with mortality. Although there is no universal agreement on a cut-off point for determining the severity of COVID-19, most studies used a cut-off of 10 mg/L (Huang et al., 2020).

This study has several limitations. The study had a relatively small sample and was observational in nature. Some of the clinical features and co-morbidities were reported as 'unknown'. It was a single-centre study, and external validity is required to support the widespread use of the findings. A larger sample size may improve the statistical power of the study. However, the findings have significant implications to better understand clinical prediction of adverse outcome among severe COVID-19 patient admitted in the ICU.

Conclusion

This study found that demographic, clinical and co-morbidity variables were not significantly associated with mortality among patients with COVID-19 admitted to the ICU during the second wave in South Africa. However, mortality was associated with D-dimer and HCO3std levels. These findings may help aid development of a possible risk score to improve the identification of patients at high risk of mortality in the ICU, and improve clinical decision-making in medical practice.

Declaration of Competing Interest

None declared.

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Ethical approval and consent to participate

Ethical approval and waiver of consent were obtained from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University and Research Ethics Committee of the Tygerberg Hospital, Ethics Approval No. N20/04/002_COVID-19.

Availability of data and material

The data presented in this study are available from the corresponding author upon request.

Author contributions

PSN: Project initiation and coordination.
PSN, UL, BA and CFK: Study design.
VDN, NB, AZ and LNS: Data acquisition.
LNS and AY: Statistical analyses.
UL, PSN, CFK, JLT and LNS: Drafting of manuscript.
UL, BA, CFK, LNS, EI, AEZ, TEM, RTE, ZCC, HP, JT, AP, EHD, FR, TRJ, VDN, AY, JLT, NB, MMA, AZ and PSN: Reviewed and revised the manuscript.
All authors read and approved the final manuscript.

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