The association between comorbid conditions and CD4+ T-cell counts with in-hospital mortality of patients with moderate to critical COVID-19 disease

C de Swardt, MB ChB; **M de Villiers,** MB ChB, FCP (SA); **D G van Zyl,** FCP (SA), MSc (Clin Epi)

Department of Internal Medicine, Kalafong Hospital, University of Pretoria, South Africa

Corresponding author: *C de Swardt (camilladeswardt@gmail.com)*

Background. COVID-19 presents with variable severity, and identifying accessible prognostic markers is critical in resource-limited settings such as South Africa (SA), where the prevalence of HIV may influence immune response and outcomes.
Objectives. To assess the association between CD4+ T-cell count and in-hospital mortality among patients with moderate to severe COVID-19 infection in SA, with a focus on specific comorbid conditions.
Methods. This cross-sectional analytical study analysed data from the first COVID-19 wave, using an electronic database compiled during the first wave of the epidemic as well as clinical records. During this period, 336 patients with moderate to critical COVID-19 were admitted to Kalafong Provincial Tertiary Hospital in Pretoria, SA. The analysis included only those patients in whom CD4+ T-cell counts (n=270) were done. Mean CD4+ T-cell counts were compared between survivors and non-survivors using non-parametric statistics. Logistic regression was performed to adjust for confounders, with survival status as the outcome variable.
Results. Sixty-nine of the 270 patients (26%) died. Mortality rates by severity of COVID were moderate (7/49, 14.3%), severe (55/211, 26.1%) and critical (7/10, 70%) (p=0.001). Patients who were positive for HIV had significantly higher mortality (19/52, 36.5%) than HIV-negative patients (50/218, 22.9%) (p=0.0436). Non-survivors had significantly lower CD4+ T-cell counts (p<0.001). After adjusting for age, hypertension, diabetes, pre-diabetes, renal disease, critical COVID-19 disease and HIV status, the CD4+ T-cell count remained significantly lower in non-survivors (p<0.001).
Conclusion. In patients with moderate to critical COVID-19 disease, lower CD4+ T-cell counts were significantly associated with mortality, suggesting that this may serve as a useful marker for predicting outcomes.

Keywords: COVID-19, CD4+ T-cell count, prognostic marker, HIV, comorbidities, mortality, resource-limited settings

S Afr Med J 2025;115(10):e2793. https://doi.org/10.7196/SAMJ.2025.v115i10.2793

SARS-CoV-2, an enveloped positive-stranded RNA virus, is responsible for COVID-19 infection. First identified in Wuhan, China, in 2019, it triggered a global pandemic.[1] As of 28 April 2024, >775 million cases and >7 million deaths had been reported globally by the World Health Organization (WHO), with South Africa (SA) accounting for >4 million cases and 100 000 deaths.[2,3] COVID-19 has a variable clinical course, ranging from asymptomatic cases to severe pneumonia, with complications such as septic shock, multi-organ failure and death. Although >80% of infected individuals experience mild symptoms and recover fully, severe cases during the pandemic strained healthcare systems, particularly in resource-limited settings during outbreaks. Identifying prognostic factors is crucial for guiding clinical care, resource allocation and appropriate patient referral to improve outcomes.[4]

A global systematic review and meta-analysis by Booth *et al.*[5] in March 2021 identified common risk factors for severe COVID-19, including: age >75 years, male sex, severe obesity and active cancer. The review identified 76 studies published between 1 January 2020 and 7 July 2020 across 14 countries, including >17 million people. The Centers for Disease Control and Prevention (CDC) list additional risk factors such as chronic lung/liver and kidney disease, cystic fibrosis, dementia, diabetes (type 1 and 2), disabled persons, cardiac and cerebrovascular disease, HIV infection and other immune compromised states, mental health conditions including substance use disorders, pregnancy, sickle cell disease/thalassaemia, smoking and tuberculosis.[6] Laboratory markers predicting severe COVID-19 and mortality include: elevated C-reactive protein, lactate dehydrogenase, D-dimer and certain cytokines such as interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α).[7-29] Reduced counts of total lymphocytes, CD3+, CD4+ and CD8+ T-cells have also been associated with worse outcomes.[7-29] Given the role of T-lymphocytes in the adaptive immune response to viral infections,[11] including COVID-19, there has been significant interest in the relationship between cytokine profiles, lymphocyte subsets and disease severity. With regard to T-cell subsets, there has been statistically significant evidence from multiple studies that less expression of CD4+ and CD8+ T-cells in blood at baseline diagnosis of COVID-19 relates to severity of disease and mortality.[7,8,10,15,20,27-31]

SA, with its limited resources and high burden of HIV, presents a unique setting for this research. Some of the markers mentioned that have been shown to predict severity of COVID-19, such as IL-6, are not freely accessible in SA due to lack of resources. However, CD4+ T-cell count is accessible and more affordable. Few studies have explored the relationship between baseline CD4+ T-cell counts and COVID-19 outcomes, particularly in the context of HIV, a disease that, over time, also results in a low CD4+ T-cell count if untreated. While some studies in SA have documented CD4+ T-cell counts in the context of COVID-19 and HIV,[32,33] they have limitations, such as not measuring baseline counts or not including HIV-negative patients. They also did not investigate the relationship between the CD4+ T-cell count and mortality as part of their studies.

The present study aimed to investigate the association between absolute CD4+ T-cell count and percentage with in-hospital mortality among patients with moderate to critical COVID-19 pneumonia in an SA setting. The goal was to assess whether CD4+ T-cell counts could serve as a useful marker for predicting disease severity, especially in relation to common comorbidities such as HIV, diabetes and hypertension.

Methods

A cross-sectional analytical study was conducted at Kalafong Provincial Tertiary Hospital (KPTH) in Pretoria, SA. The study included adult patients (defined as those aged ≥13 years at KPTH) who were admitted during the first wave of the COVID-19 pandemic, from 20 May 2020 to 30 September 2020, with moderate, severe and critical COVID-19. Severity definitions followed the UK National Institute of Health's guidelines for SARS-CoV-2 infection.[34] COVID-19 was confirmed via reverse-transcriptase-polymerase chain reaction by the National Health Laboratory Services (NHLS) of SA. Patients with asymptomatic or mild disease admitted solely for isolation, and those without CD4+ T-cell count data or with incomplete records, were excluded. The study adhered to the principles of the Declaration of Helsinki. Data were primarily sourced from a database created by the hospital's Department of Internal Medicine during the first COVID-19 wave. For patients with insufficient information on the database, medical records were reviewed directly from hospital files or the NHLS TrakCare system.

Appropriate data were collected that included all of the following: date of birth; date of admission; sex; comorbidities; presence of obesity; haemoglobin A1C (HbA1c), where applicable; absolute CD4+ T-cell count, and percentage with the date of testing; COVID-19 disease severity; patient outcome; and date of patient outcome. Comorbid conditions were taken into account if known, or if newly diagnosed during admission to the COVID-19 ward. In the case of known, newly diagnosed or suspected diabetes, a HbA1C was performed and recorded. A HbA1c of ≥6.5% was considered confirmatory of diabetes mellitus, whereas a HbA1c of ≥6.0% - 6.4% was considered pre-diabetic. A HbA1c of <6.0% was considered normal. The type of diabetes mellitus (type 1 v. type 2) was not recorded. In light of the high risk of contracting or spreading COVID-19 disease, blood was taken once from the patients at admission, and included a baseline panel determined by the COVID-19 unit. Owing to the high prevalence of HIV in the population served by the hospital, HIV was included as one of the admission tests after consent was obtained. It was assumed at that time that HIV (an immune-deficient state) would be a risk factor for more severe disease. In light of the profound lymphopenia that had already been described in the literature, as well as anecdotal evidence linking a low CD4+ T-cell count and disease severity noted by the Kalafong COVID-19 unit, an early decision was made to measure CD4+ T-cell counts on all patients admitted to the unit. The available CD4+ T-cell count and percentage were only included if taken within 24 hours of admission, in order to give information on a baseline CD4+ T-cell count. The method used by the NHLS to determine the number of CD4+ T-cells and its percentage during this period was fluorescence-activated cell sorting analysis by flow cytometry. On admission, patients were classified as 'obese' or 'not obese' at the admitting doctor's discretion, and recorded in the electronic database. Formal weight and height measurements were not taken owing to patients' limited mobility and oxygen dependency. Patients were classified as 'survivors' if discharged from the COVID-19 wards, whether to home or another ward for further care. Those who died while in the COVID-19 unit were classified as 'non-survivors.' The outcome date was recorded, and in-hospital duration of stay was determined from admission to discharge date or date of death in the COVID-19 unit.

Ethical approval

This study was approved by the ethics committee of the Faculty of Health Sciences of the University of Pretoria (ref. no. 519/2022). Approval was obtained and permission granted by the custodian of the COVID-19 units' electronic database as well as the KPTH Research Committee for the investigator to access the data.

Statistical analysis

The primary aim of this study was to determine whether CD4+ T-cell counts differed between survivors and non-survivors of COVID-19 at KPTH. Demographic and descriptive statistics were compared between the two groups using appropriate statistical tests. The mean CD4+ T-cell count between groups was compared using the Mann-Whitney U test. Logistical regression was done to adjust for predictors of mortality and independence of these predictors, which included CD4+ T-cell count. Univariate analysis included clinical predictors of mortality and CD4+ T-cell count. All predictors with a $p<0.15$ in the univariate analysis were included in multivariate analysis. The multivariate analysis was simplified by removing variables with significant collinearity or correlation to create the most parsimonious model, both with and without the CD4+ T-cell count. All logistic regression models used mortality as the dependant variable. A *post hoc* power calculation was performed for the difference in CD4+ T-cell count between patients who survived and those who died.

Given SA's high HIV prevalence, we compared outcomes between HIV-positive and HIV-negative patients using a χ^2 test. An analysis of demographic and clinical characteristics, disease severity and CD4+ T-cell count and percentage between survivors and non-survivors was done. Non-parametric comparisons of CD4+ T-cell counts were performed between patients with and without diabetes, as well as between patients with and without hypertension, to determine the influence on mortality. CD4+ T-cell count differences across varying disease severities were explored. A power calculation was also conducted separately for HIV-positive and HIV-negative patients for the difference in CD4+ T-cell counts between these two groups.

Results

Of the 336 patients admitted to KPTH with COVID-19 disease during the first wave in SA, 270 fulfilled the inclusion criteria. Sixty-six patients were excluded because they did not have a CD4+ T-cell count available. Demographic and descriptive characteristics of the patients are shown in Table 1.

The inpatient mortality rate was 26% (69 of 270 patients). Mortality across disease severity categories showed an increased trend of death with severity status. Deaths per category were respectively: moderate: 7/49 (14.3%); severe: 55/211 (26.1%); and critical: 7/10 (70%) ($p=0.001$). Mortality rates did not differ significantly by sex: 22/140 females (15.7%) v. 38/130 males (29.2%) ($p=0.182$). Age was significantly higher in those who died (median (interquartile range (IQR) 62 (55 - 69.5) years) compared with survivors (median (IQR) 52 (41 - 65 years) ($p<0.001$). Investigation into the CD4+ T-cell count revealed that the patients who died had a statistically significantly lower absolute CD4+ T-cell count ($p<0.001$). The 69 deceased patients had a median CD4+ T-cell count of 275 cells/mm^3 (34.35%) and a mean (standard deviation (SD) CD4+ T-cell count of 297 (205), compared with a median of 440 cells/mm^3 (33.93%) and a mean (SD) of 457 (263) in the 201 survivors. A *post hoc* power calculation was performed to assess the difference in CD4+ T-cell count between

patients who died and those who survived. The power to detect a significant difference between these groups was 99%, assuming a true difference exists and an α threshold of 0.05.

Absolute CD4+ cell counts did not differ significantly between patients with and without diabetes mellitus and hypertension overall ($p>0.05$). However, a significant difference was observed between obese and non-obese patients, with obese patients having higher mean CD4+ T-cell counts (144.11 v. 117.48 cells/mm^3, $p=0.008$). There was no statistically significant difference in absolute CD4+ T-cell count across the different COVID-19 disease severity categories. Univariate logistic regression identified age, hypertension, diabetes, pre-diabetes, renal disease, HIV, critical COVID-19 disease severity and absolute CD4+ T-cell count as predictors of death ($p<0.15$), to be included in the multivariate regression. Notably, sex, obesity, HbA1c levels and malignant diseases (classified under 'other' comorbidities in Table 1) did not meet the criteria for significance for inclusion in the multivariate model.

After adjustment for confounding variables: age (odds ratio (OR) 0.962, confidence interval (CI) 0.935 - 0.989, $p= <0.001$) hypertension (OR 0.751, CI 0.370 - 1.525, $p=0.428$), diabetes (OR 0.968, CI 0.461-2.034, $p=0.932$), pre-diabetes (OR 13.528, CI 1.584 - 115.53, $p=0.17$), HIV status (OR 0.546, CI 0.370 - 1.525, $p=0.176$), renal disease (OR 0.605, CI 0.229 - 0.594, $p=0.309$), and critical COVID-19 disease severity (OR 0.042, CI 0.007 - 0.272, $p<0.001$), CD4+ T-cell count remained significantly inversely related to COVID-19 disease mortality (OR 1.004, CI 1.002 - 1.005, $p<0.001$).

Given the high prevalence of HIV in SA, the characteristics and outcomes were analysed separately for HIV-positive and HIV-negative patients (Table 2). Among the 270 patients, 218 were HIV-negative and 52 were HIV-positive. HIV-positive patients had a significantly higher mortality rate (19/52, 36.5%l CI 23.6% - 51.0%) compared with the HIV-negative patients (50/218, 22.9%; CI 17.5% - 29.1%; $p=0.043$). In both the HIV-positive and HIV-negative patient groups, the CD4+ T-cell count was lower in the patients who died (Fig. 1). A power calculation was also conducted separately for HIV-positive and HIV-negative patients to assess the difference in CD4+ T-cell counts between these two groups. In the HIV-positive group, the power to detect a difference in CD4+ T-cell count between survivors and non-survivors was 78%, while in the HIV-negative group, it was 97% (α threshold 0.05).

Discussion

Our study demonstrated that patients with moderate to critical COVID-19 who died had significantly lower absolute CD4+ T-cell counts, regardless of other risk factors or comorbidities. This reduction was observed in both HIV-positive and HIV-negative populations. Consistent with our findings, several studies have reported that lower baseline CD4+ T-cell counts at COVID-19 diagnosis are associated with increased morbidity and mortality, although most were conducted in regions with low HIV prevalence.[7,8,10,15,20,27-31] In SA, one study on HIV-positive patients confirmed that lower CD4+ T-cell counts were linked to increased mortality, but it lacked data on HIV-negative individuals.[32] Another SA study found that a CD4+ T-cell count <200 cells/μL was associated with COVID-19 death in HIV-positive patients, though only 33% had their CD4+ count measured, and it was not always a baseline measurement. No data were provided for the HIV-negative population.[33]

Although both CD4+ T-cell count and disease severity independently related to mortality, no statistically significant difference in CD4+ T-cell count trend could be demonstrated across different levels of disease severity. This was unexpected, as most literature links lower CD4+ T-cell counts with both increased severity and mortality.[7,8,10,15,20,27,28,30,31] This discrepancy may be due to the distribution of our study population, where 78.1% (211/270) were classified as having severe disease, 18.1% (49/270) as moderate, and only 3.7% (10/270) as critical. Additionally, CD4+ T-cell percentage was not significantly related to mortality. Given that other studies have shown declines in both CD4+ and CD8+ T-cells without significant changes in the CD4:CD8 ratio in COVID-19,[11] we did not anticipate CD4+ T-cell percentage to have prognostic value.

Table 1. Description of patients (*N*=270)

Characteristic	Mean (SD)*	*n* (%)
Sex		
Male		140 (51.8)
Female		130 (48.1)
Age, years	54.9 (14.6)	
Comorbidity		
Obesity		177 (65.5)
Diabetes		163 (60.4)
Pre-diabetes		31 (11.5)
Hypertension		133 (49.3)
HIV infection		52 (19.3)
Renal disease		24 (8.9)
Other		135 (50.0)
HbA1c (%) (*n*=234), median (IQR)	7.1 (3.6 - 18.8)	
COVID-19 disease severity		
Moderate		49 (18.1)
Severe		211 (78.1)
Critical		10 (3.7)
Absolute CD4 T-cell count (cells/mm^3), median (IQR)	365 (243 - 553)	
CD4 T-cell percentage (%), median (IQR)	33.95 (25.82 - 42.70)	
Duration of stay, days (*n*=253)†	6.0 (3 - 11)	

IQR = interquartile range; SD = standard deviation; HbA1c = haemoglobin A1C.
*Unless otherwise indicated.
†Only 253 patients had complete data available to enable calculation of the duration of stay.

The overall mortality rate was 26%, and the mortality in HIV-positive patients was significantly higher than in HIV-negative patients. In addition to low CD4+ T-cell count, factors significantly associated with increased mortality included age, hypertension, pre-diabetes, diabetes, renal disease and HIV – conditions recognised by the CDC and WHO as risk factors for severe COVID-19.[2,6] Although both organisations classify HIV infection as a risk factor, studies have shown mixed results on whether HIV increases the severity of COVID-19. An epidemiological study early in the first wave of COVID-19 in SA investigated the pattern of mortality and found that, despite the high prevalence of HIV, it was not a common comorbidity among those who died from COVID-19.[35] A retrospective cohort study at a Johannesburg, SA, state hospital involving 384 patients found no significant difference in mortality between HIV-positive and HIV-negative patients.[32] A 2021 national cohort study of nearly 220 000 individuals in SA with an HIV prevalence of 19% showed that HIV (and tuberculosis), along with age, sex and other comorbidities, moderately increased the risk of in-hospital mortality.[36] A recent global systematic review by Favara *et al.*[37] involving 28 studies found no difference in mortality risk between HIV-positive and HIV-negative patients. None of these studies examined the association between baseline CD4+ T-cell count and mortality in either HIV-positive and HIV-negative patients. This raises the question of whether the varying risks of severe COVID-19 in HIV-positive patients across studies are linked to their baseline CD4+ T-cell count before COVID-19 infection. A low baseline count may further decline during COVID-19

Table 2. Characteristics of HIV-positive v. HIV-negative patients who died

Characteristic	HIV-positive (*n*=19), *n* (%)*	HIV-negative (*n*=50), *n* (%)*	*p*-value
Sex			
Male	11/27 (40.7)	27 /103 (26.2)	0.065
Female	8/25 (32)	23/115 (20)	0.192
Age, years, mean (SD)	52.26 (12.92)	63.50 (9.15)	<0.001
Comorbidities			
Diabetes	10/25 (40)	39/138 (28.3)	0.24
Pre-diabetes	0/4 (0)	1/27 (3.7)	0.7
Hypertension	11/20 (55)	33/113 (29.2)	0.024
Obesity	9/21 (42.9)	36/156 (23.1)	0.051
Renal disease	5/20 (25)	14/71 (19.7)	0.608
COVID-19 disease severity			
Moderate	4/17 (23.5)	3/32 (9.4)	0.184
Severe	14/33 (42.4)	41/178 (23.0)	0.02
Critical	1/2 (50)	6/8 (75)	0.513
Absolute CD4 T-cell count (cells/mm^3), median (IQR)	158 (35 - 303)	289 (226 - 447)	0.003
CD4 T-cell percentage (%), median (IQR)	18.83 (9.23 - 28.89)	36.44 (27.0 - 41.05)	<0.001
HbA1c (%), median (IQR)	6.5 (5.9 - 8.9)	7.5 (6.8 - 9.8)	0.095
Duration of stay (days), median (IQR)	2 (1 - 7)	4 (2 - 7)	0.175

SD = standard deviation; IQR = interquartile range; HbA1c = haemoglobin A1C.
*Unless otherwise indicated.

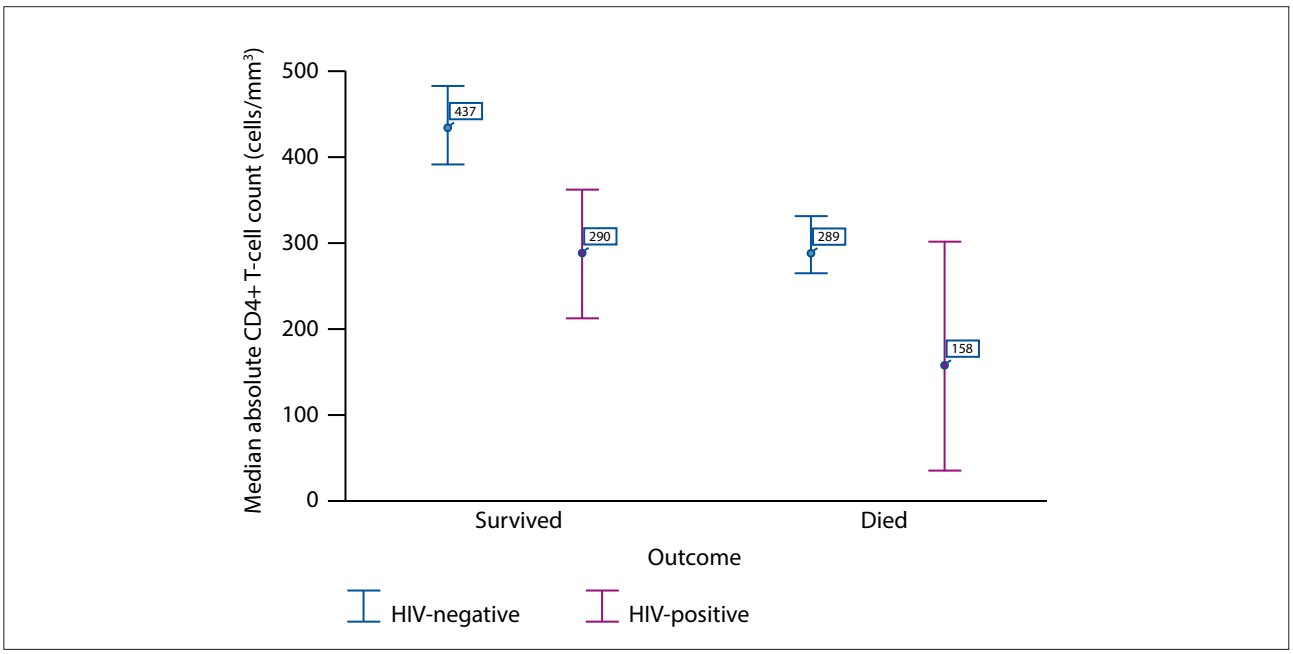

Fig. 1. Median and 95% confidence interval of absolute CD4+ T-cell count by outcome in HIV categories.

as part of the pathogenesis of the disease,[11] leading to more severe disease and higher mortality. This suggests that the risk factor may not be HIV itself, but rather a low CD4+ T-cell count. We analysed the characteristics and comorbidities of HIV-positive and HIV-negative groups separately to assess whether statistically significant differences existed between the characteristics of patients who died in these groups. The HIV-positive patients were significantly younger and had lower CD4+ T-cell counts and percentages. Given the pathogenesis and natural history of HIV, lower CD4+ T-cell counts and reduced life expectancy in HIV-positive individuals compared with the general population were anticipated.

Sex, obesity and chronic obstructive pulmonary disease (COPD) were not statistically significant risk factors for mortality in our study, contrary to other literature that links male sex, obesity and respiratory disease with worse outcomes and higher in-hospital mortality.[5,23] The CDC also recognises these as risk factors for severe COVID-19.[6] The lack of significance for COPD in our study may be due to the limited sample size (10/270, 3.7%). Surprisingly, the CD4+ T-cell count was statistically significantly higher in the obese group overall compared with the non-obese group. After adjusting for other variables in the multivariate analysis, obesity was not a significant predictor of mortality in our study. However, the diagnosis of obesity was limited by the informal method of assessment, relying on the physician's discretion rather than formal measurements, which may have led to inaccuracies.

Other limitations include the fact that this is a single-centre cross-sectional analysis, and therefore the findings are specific to our location, and further research is needed to identify prognostic markers for COVID-19 in SA and other regions with a high HIV burden. Furthermore, the data were drawn from an existing database, limiting our analysis to the available information. For example, we documented a single CD4+ T-cell count within the first 24 hours of admission, without accounting for the timing of symptom onset. Repeated CD4+ T-cell measurements throughout the course of COVID-19 disease could have provided more accurate insights into severity and clinical progression. Additionally, our study only included patients from the first wave of COVID-19 in SA, and characteristics and outcomes may have varied in subsequent waves due to different viral strains. We also focused on patients with moderate, severe and critical disease, excluding those with asymptomatic or mild disease. Finally, our classification of survivor status did not consider outcomes post discharge from the COVID-19 ward.

Conclusion

A low CD4+ T-cell count in the setting of moderate to critical COVID-19 disease was statistically significantly lower in patients who died, irrespective of comorbidities present – including HIV. CD4+ T-cell count may therefore be a useful marker to predict outcomes, and thereby assist in guiding clinical care and resource allocation.

AI contribution. During the preparation of this work the authors used ChatGPT in order to edit and shorten this document for scientific language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Data availability. Data are available from the authors upon reasonable request.

Declaration. This publication was a requirement for CdeS's MMed (Internal Medicine) degree from the University of Pretoria.

Acknowledgements. The authors would like to acknowledge the Department of Internal Medicine at Kalafong Provincial Tertiary Hospital for their exceptional dedication and resilience, and commendable efforts in caring for patients and advancing clinical knowledge during the COVID-19 pandemic.

Author contributions. CdS and MdV formulated the hypothesis of the study. CdS, MdV and DGvZ developed the design of the study. CdS formulated a research protocol which was submitted and approved by the both the University of Pretoria and Kalafong Hospital ethics committees. CdS conducted the collection of data and was responsible for data curation and validation. DGvZ performed the data and statistical analysis. CdS drafted the manuscript. All authors provided comments on the manuscript and all authors accepted the final version.

Funding. This study received no specific funding. The blood tests performed had been done at the time of the COVID-19 outbreak and were checked retrospectively, and therefore no extra cost was incurred.

Conflicts of interest. None.

1. National Institute for Communicable Diseases. COVID-19. Johannesburg: NICD, 2024. https://www.nicd.ac.za/diseases-a-z-index/disease-index-covid-19/ (accessed 14 July 2024).
2. World Health Organization. Weekly epidemiological update on COVID-19. Geneva: WHO, 2024. https://www.who.int/publications/m/item/covid-19-epidemiological-update-edition-167 (accessed 14 July 2024).
3. Worldometer. Coronavirus tracker: South Africa. Worldometer, 2024. https://www.worldometers.info/coronavirus/country/south-africa/ (accessed 26 May 2024).
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239-1242. https://doi.org/10.1001/jama.2020.2648
5. Booth A, Reed AB, Ponzo S, et al. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. PLoS ONE 2021;16(3):e0247461. https://doi.org/10.1371/journal.pone.0247461
6. Centers for Disease Control and Prevention. Assessing risk factors for severe covid-19 illness. Atlanta: CDC, 2024. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (accessed 14 July 2024).
7. Akbari H, Tabrizi R, Lankarani KB, et al. The role of cytokine profile and lymphocyte subsets in the severity of coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Life Sci 2020;258:118167. https://doi.org/10.1016/j.lfs.2020.118167
8. Belaid B, Lamara Mahammad L, Mihi B, et al. T-cell counts and IL-6 concentration in blood of North African COVID-19 patients are two independent prognostic factors for severe disease and death. J Leukoc Biol 2022;111(1):269-281. https://doi.org/10.1002/JLB.4COVA1020-703R
9. Fu YQ, Sun YL, Lu SW, Yang Y, Wang Y, Xu F. Effect of blood analysis and immune function on the prognosis of patients with COVID-19. PLoS ONE 2020;15(10):e0240751. https://doi.org/10.1371/journal.pone.0240751
10. Hu D, Li L, Shi W, Zhang L. Less expression of CD4(+) and CD8(+) T-cells might reflect the severity of infection and predict worse prognosis in patients with COVID-19: Evidence from a pooled analysis. Clin Chim Acta 2020;510:1-4. https://doi.org/10.1016/j.cca.2020.06.040
11. Jesenak M, Brndiarova M, Urbancikova I, et al. Immune parameters and COVID-19 infection – associations with clinical severity and disease prognosis. Front Cell Infect Microbiol 2020;10:364. https://doi.org/10.3389/fcimb.2020.00364
12. Li M, Guo W, Dong Y, et al. Elevated exhaustion levels of NK and CD8(+) T cells as indicators for progression and prognosis of COVID-19 disease. Front Immunol 2020;11:580237. https://doi.org/10.3389/fimmu.2020.580237
13. Luo M, Liu J, Jiang W, Yue S, Liu H, Wei S. IL-6 and CD8+ T-cell counts combined are an early predictor of in-hospital mortality of patients with COVID-19. JCI Insight 2020;5(13):e139024. https://doi.org/10.1172/jci.insight.139024
14. Zhang P, Du W, Yang T, et al. Lymphocyte subsets as a predictor of severity and prognosis in COVID-19 patients. Int J Immunopathol Pharmacol 2021;35:20587384211048567. https://doi.org/10.1177/20587384211048567
15. Zhang X, Tan Y, Ling Y, et al. Viral and host factors related to the clinical outcome of COVID-19. Nature 2020;583(7816):437-440. https://doi.org/10.1038/s41586-020-2355-0
16. Zhao Z, Xie J, Yin M, et al. Interleukin-6 and severity of COVID-19 patients in Hefei, China. Med Mal Infect 2020;50(7):629-631. https://doi.org/10.1016/j.medmal.2020.06.005
17. Bivona G, Agnello L, Ciaccio M. Biomarkers for prognosis and treatment response in COVID-19 patients. Ann Lab Med 2021;41(6):540-548. https://doi.org/10.3343/alm.2021.41.6.540
18. Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: A systematic review and meta-analysis. Rev Med Virol 2020;30(6):1-9. https://doi.org/10.1002/rmv.2141
19. Hariyanto TI, Japar KV, Kwenandar F, et al. Inflammatory and hematologic markers as predictors of severe outcomes in COVID-19 infection: A systematic review and meta-analysis. Am J Emerg Med 2021;41:110-119. https://doi.org/10.1016/j.ajem.2020.12.076
20. Li Q, Xu W, Li W, Huang C, et al. Dynamic differences of immunological parameters between severe and non-severe COVID-19 patients. Discov Med 2021;31(163):79-87.
21. Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalisations: Systematic review and meta-analysis. BMJ Evid Based Med 2021;26(3):107-108. https://doi.org/10.1136/bmjebm-2020-111536
22. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis 2020;221(11):1762-1769. https://doi.org/10.1093/infdis/jiaa150
23. Xiang G, Xie L, Chen Z, et al. Clinical risk factors for mortality of hospitalised patients with COVID-19: Systematic review and meta-analysis. Ann Palliat Med 2021;10(3):2723-2735. https://doi.org/10.21037/apm-20-1278
24. Zeng F, Huang Y, Guo Y, et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis 2020;96:467-474. https://doi.org/10.1016/j.ijid.2020.05.055
25. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130(5):2620-2629. https://doi.org/10.1172/jci137244

26. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020;27(6):992-1000. https://doi.org/10.1016/j.chom.2020.04.009
27. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020;71(15):762-768. https://doi.org/10.1093/cid/ciaa248
28. He R, Lu Z, Zhang L, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. J Clin Virol 2020;127:104361. https://doi.org/10.3389/fcimb.2020.00364
29. Hedayati-Ch M, Ebrahim-Saraie HS, Bakhshi A. Clinical and immunological comparison of COVID-19 disease between critical and non-critical courses: A systematic review and meta-analysis. Front Immunol 2024;15:1341168. https://doi.org/10.3389/fimmu.2024.1341168
30. Iwamura APD, Tavares da Silva MR, Hümmelgen AL, et al. Immunity and inflammatory biomarkers in COVID-19: A systematic review. Rev Med Virol 2021;31(4):e2199. https://doi.org/10.1002/rmv.2199
31. Zahornacky O, Rovnakova A, Surimova M, Porubcin S, Jarcuska P. Identifying mortality predictors in hospitalised COVID-19 patients: Insights from a single-center retrospective study at a university hospital. Microorganisms 2024;12(5):1032. https://doi.org/10.3390/microorganisms12051032
32. Venturas J, Zamparini J, Shaddock E, et al. Comparison of outcomes in HIV-positive and HIV-negative patients with COVID-19. J Infect 2021;83(2):217-227. https://doi.org/10.1016/j.jinf.2021.05.020
33. Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases SA. Risk factors for coronavirus disease 2019 (COVID-19) death in a population cohort study from the Western Cape Province, South Africa. Clin Infect Dis 2020;73(7):e2005-e2015. https://doi.org/10.1093/cid/ciaa1198
34. National Institutes of Health. Clinical spectrum of SARS-CoV-2 infection. Bethesda: NIH, 2024. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ (accessed 14 July 2024).
35. Pillay-van Wyk V, Bradshaw D, Groenewald P, et al. COVID deaths in South Africa: 99 days since South Africa's first death. S Afr Med J 2020;110(11):1093-1099. https://doi.org/10.7196/samj.2020.v110i11.15249
36. Jassat W, Cohen C, Tempia S, et al. A national cohort study of COVID-19 in-hospital mortality in South Africa: The intersection of communicable and non-communicable chronic diseases in a high HIV prevalence setting. medRxiv 2021. https://doi.org/10.1101/2020.12.21.20248409
37. Favara G, Barchitta M, Maugeri A, Faro G, Agodi A. HIV infection does not affect the risk of death of COVID-19 patients: A systematic review and meta-analysis of epidemiological studies. J Glob Health 2022;12:05036. https://doi.org/10.7189/jogh.12.05036

Received 1 November 2024; accepted 5 August 2025.