The utility of procalcitonin as a biomarker of hospital-acquired infection in severe COVID-19

C Schmidt,[1] MB ChB; **P S Nyasulu,**[2,3] MSc (Epidemiology), PGDip (Epidemiology), PhD; **I Fwemba,**[4] PhD (Biostatistics); **U Lalla,**[1] MB ChB, FCP (SA), FCRP, Cert Critical Care (SA), Cert Pulmonology (SA); **B W Allwood,**[1] MB ChB, FCP (SA), Cert Pulmonology (SA), PhD; **A Parker,**[5] MB ChB, FCP (SA), Cert ID (SA), PhD; **J J Taljaard,**[4] MB ChB, MMed (Int); **L N Sigwadhi,**[6] MSc (Biostatistics); **J L Tamuzi,**[2] MD, MSc, MPH; **A E Zemlin,**[6] MB ChB, FC Path (SA) Chem, MMed (Chem), PhD; **R T Erasmus,**[6] MBBS, FMCPath, FACB, DABCC, DHSM; **C F N Koegelenberg,**[1] MB ChB, FCP (SA), FCRP, Cert Pulmonology (SA), PhD

[1] *Division of Pulmonology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa*

[2] *Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa*

[3] *Division of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

[4] *School of Public Health, University of Zambia, Lusaka, Zambia*

[5] *Division of Infectious Diseases, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa*

[6] *Division of Chemical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University and National Health Laboratory Service – Tygerberg Hospital, Cape Town, South Africa*

Corresponding author: *C Schmidt (charle21.cs@gmail.com)*

Background. Hospital-acquired infection (HAI) in patients with COVID-19 admitted to the intensive care unit (ICU) is associated with increased mortality. The 'cytokine storm' associated with COVID-19 leads to extreme elevation of inflammatory biomarkers, including C-reactive protein (CRP). Procalcitonin (PCT) has been shown to be more discriminative than CRP in distinguishing HAI from other inflammatory processes.

Objectives. To investigate the utility of PCT in detecting HAI in patients with severe COVID-19.

Methods. Clinical and laboratory data from all patients admitted to a dedicated ICU with confirmed severe COVID-19 from 1 April 2020 to 31 August 2020 were prospectively captured. HAI was confirmed by serial PCT and CRP measurements, as well as microbiological data (positive microbiological cultures in clinical context). Data from patients who were on antibiotics on ICU admission, had a positive culture for a presumed pathogen during the first 48 hours of ICU admission, or already had suspected or proven HAI on admission were excluded. Optimal cut-offs with the highest sensitivity and specificity were determined. The discriminative power of PCT was assessed for each outcome, using receiver operating characteristic (ROC) analysis describing the area under the curve. Similarly, negative predictive values (NPVs) and positive predictive values (PPVs) were determined. The sensitivity and specificity for different PCT cut-off levels were calculated.

Results. Of 92 patients, 35 had confirmed HAI, which was significantly associated with mechanical ventilation ($p<0.001$) and mortality ($p<0.001$). ROC analysis demonstrated that a threshold PCT level of 0.22 µg/L resulted in 97% sensitivity and 40% specificity for predicting HAI. Similarly, sensitivity and specificity for CRP were 91.4% and 38.6%, respectively, when the CRP level was 133 mg/L. In patients with a PCT level <0.25 µg/L, the NPV was 92%, whereas for PCT levels >1.00 µg/L, the PPV was >50%. For PCT levels >40 µg/L, the PPV was 100%.

Conclusion. During HAI, PCT levels >1.00 µg/L had a moderate PPV of 52%, whereas levels <0.26 µg/L ruled out HAI with an NPV of 92%. With increased PCT values, the PPV rose to 100%, making it a better biomarker than CRP.

Keywords. Procalcitonin, SARS-CoV-2, COVID-19.

Afr J Thoracic Crit Care Med 2024;30(4):e1617. https://doi.org/10.7196/AJTCCM.2024.v30i4.1617

Study synopsis

What the study adds. During an episode of hospital-acquired infection (HAI) in patients with severe COVID-19, procalcitonin (PCT) levels >1.00 µg/L had a moderate positive predictive value (PPV) of 52%, whereas levels <0.26 µg/L had a negative predictive value (NPV) of 92% for proven HAI. For PCT levels >40 µg/L, the PPV was 100%.

Implications of the findings. At levels <0.26 µg/L, PCT had an NPV >90%. This 'rule-out' characteristic of PCT may be especially valuable in scenarios of diagnostic equipoise with regard to the presence of bacterial co-infection. Clinicians should take care to not unjustifiably associate elevations in PCT levels with the presence of bacterial co-infection, unless levels are extremely high, in which case the PPV rises significantly.

Reports from many international and local studies in the early days of the COVID-19 pandemic showed that bacterial co-infection was relatively uncommon at initial presentation.[1,2] Hospital-acquired infection (HAI) in patients admitted to an intensive care unit (ICU) was also clearly shown to be associated with increased mortality.[1]

In any patient admitted to an ICU, several clinical, radiological and laboratory markers may indicate the presence of an HAI. A major challenge with SARS-CoV-2-infected patients is that the now well-recognised 'cytokine storm' leads to, among other manifestations, fever and extreme elevation of inflammatory biomarkers, including C-reactive protein (CRP).[3]

Procalcitonin (PCT) is a glycoprotein, the pro-peptide of calcitonin devoid of hormonal activity. Under normal circumstances, it is produced in the C-cells of the thyroid gland. In healthy humans, serum PCT levels are undetectable (<0.1 µg/L).[4] Prior to the COVID-19 pandemic, several studies demonstrated that PCT levels were more discriminative than the white blood cell count and CRP in distinguishing serious bacterial and fungal infection from other inflammatory processes.[4,5]

At the start of the present study, it was not yet clear whether bacterial co-infection would play a major role early or late in severe COVID-19. We therefore aimed to investigate the utility of PCT in detecting HAI in patients with severe COVID-19 admitted to an ICU.

Methods

Setting and study design

Clinical and laboratory data from all patients with confirmed severe SARS-CoV-2 pneumonia admitted to the dedicated COVID-19 ICU at Tygerberg Hospital, Cape Town, South Africa, from 1 April 2020 to 31 August 2020 (the first local wave) were prospectively captured as part of a multidisciplinary study collaboration. Tygerberg Hospital is a 1 380-bed tertiary referral centre that serves a population of ~3 million. The collection of data was approved by the Health Research Ethics Committee of Stellenbosch University (ref. no. N20/04/002_COVID-19). The investigators and authors had no access to information that could identify individual participants during or after data collection.

Clinical and microbiological data

Patients who had no evidence of bacterial superinfection and who were not on antibiotics on admission to the ICU were identified. Data extracted included patient demographics, comorbidities, laboratory data, serial PCT and CRP measurements, outcome, invasive ventilation, microbiological data (blood cultures, tracheal aspirate cultures, stool cultures and urine cultures) confirming infection, and date of antibiotic initiation on the basis of confirmed or suspected HAI. Data from patients who were on antibiotics on ICU admission, had a positive culture for a presumed pathogen during the first 48 hours of ICU admission, or had a suspected or known HAI on admission were excluded. The data on the first proven HAI episode were used for analysis (should more than one episode have occurred). Patients categorised as having 'suspected' sepsis never (at any point) had proven HAI.

Apart from demographic data and risk factors for severe COVID-19, the highest form of respiratory/ventilatory support (up to intubation and mechanical ventilation) and the daily clinical suspicion of HAI (according to the treating physician) were documented. 'Confirmed' HAI was supported by confirmation of positive microbiological data (positive blood, tracheal aspirate and urine cultures) excluding culture contaminants, whereas 'suspected' could not be proven by microbiological means.

All cultures were submitted to the on-site National Health Laboratory Service microbiology laboratory and processed using standard procedures. Identification and antibiotic susceptibility testing of cultured isolates involved use of the automated VITEK 2 system (bioMérieux, France), and was supplemented where necessary with the ETEST (bioMérieux, France) to confirm the minimum inhibitory concentration. Positive culture results were deduplicated based on site of sample collection, with a positive result showing the same pathogen with the same susceptibility profile within a 5-day period being considered a single episode. Organisms such as coagulase-negative staphylococci and *Bacillus cereus* were considered contaminants if they were only cultured once, or as pathogens if they were cultured more than once in the same patient in an appropriate setting (e.g. central line-associated bloodstream infection) where the attending physician deemed these cultures to be clinically significant.

PCT and CRP measurements

PCT was determined by Elecsys BRAHMS PCT (Roche Diagnostics, Germany), an electrochemiluminescence immunoassay, measured on the cobas e 601 (Roche Diagnostics, Germany). CRP was measured by means of CRP4, an immunoturbidimetric method, on the cobas c 501 (Roche Diagnostics, Germany).

Outcome measures

The primary outcome measure was proven sepsis in patients with severe COVID-19 pneumonia admitted to the COVID-19 ICU. The secondary outcome measure was suspected sepsis. Covariates such as positive culture, length of stay, age and discharge were all considered as exposure factors.

Statistical analysis

Data were analysed using R Studio 4.2.3 (R Core Team, USA). Statistical significance was set at $p<0.05$ with corresponding 95% confidence intervals (CIs). Continuous variables were expressed as means with standard deviations for normally distributed data and as medians with interquartile ranges for non-normal data. Categorical variables were expressed using frequencies and percentages. Pearson's χ^2 test of independence was used to identify associations between categorical variables and the outcomes of interest. The *t*-test was used to compare the means of continuous data where the data had a normal distribution, and the Mann-Whitney *U*-test where data did not have a normal distribution. The PCT and CRP values on the day of onset of either proven or suspected HAI were used for analyses. We used a generalised model with binomial family to fit the model on proven and suspected PCT and CRP predictors. Optimal PCT and CRP cut-offs were determined using PRO in R Studio. Optimal cut-offs were determined to be the highest value at which sensitivity and specificity were highest. These were determined for COVID-19

patients with both suspected and proven sepsis. The discriminative power of PCT and CRP was assessed for each outcome, using receiver operating characteristic (ROC) analysis describing the area under the curve (AUC). Similarly, negative predictive values (NPVs) and positive predictive values (PPVs) were also determined. The sensitivity, specificity and positive likelihood ratio for different PCT cut-off levels were calculated. To determine the prognostic accuracy of PCT and CRP at both time points, ROC curves were constructed and the AUCs were calculated together with the corresponding 95% CIs. A *p*-value <0.05 was considered statistically significant in all analyses.

Results

In total, the data on 92 patients were included in the study (Table 1). Of these, 35 patients had proven HAI confirmed by blood, tracheal aspirate or urine cultures, 25 had suspected HAI, and 32 showed no evidence of HAI. Notably, intubation, mechanical ventilation and mortality were significantly associated with both proven and suspected HAI ($p<0.001$).

ROC curve analysis of PCT and CRP yielded AUCs of 0.690 and 0.572, respectively (Figs 1 and 2). A PCT level of 0.22 µg/L demonstrated sensitivity of 97% and specificity of 40% (Table 2). For CRP, a level of 133 µg/L yielded sensitivity and specificity values of 91.4% and 38.6%, respectively (Table 3).

Table 2. Procalcitonin thresholds for different indices in patients with proven hospital-acquired infection

Threshold (µg/L)	Sensitivity	Specificity	PPV	NPV
0.24	0.94	0.40	0.48	0.92
0.26	0.94	0.42	0.49	0.92
0.93	0.73	0.58	0.51	0.78
1.01	0.73	0.60	0.52	0.79
1.27	0.61	0.62	0.49	0.72
40.63	0.03	1.00	1.00	0.63

PPV = positive predictive value; NPV = negative predictive value.

Table 3. C-reactive protein thresholds for different indices in patients with proven hospital-acquired infection

Threshold (mg/L)	Sensitivity	Specificity	PPV	NPV
47.5	1.00	0.05	0.39	1.00
56.5	1.00	0.07	0.39	1.00
207.0	0.52	0.53	0.40	0.64
437.5	0.03	0.98	0.50	0.63

PPV = positive predictive value; NPV = negative predictive value.

Table 1. Baseline (admission) characteristics and bivariate analysis of all patients

Characteristic	All (*N*=92), *n* (%)*	Proven HAI (*n*=35), *n* (%)*	Suspected HAI (*n*=25), *n* (%)*	No sepsis (*n*=32), *n* (%)*	*p*-value†	*p*-value‡
Age (years)	53.5 (11.1)	56.2 (10.4)	52.3 (10.8)	51.4 (11.8)	0.09	0.77
Sex (male)	48 (52.1)	19 (54.2)	13 (52)	16 (50)	0.81	1
Diabetes	48 (52.1)	19 (54.2)	14 (56.0)	15 (46.8)	0.63	1
Hypertension	53 (57.6)	24 (68.6)	13 (52.0)	16 (50.0)	0.14	1
Obesity	62 (67.39)	23 (65.7)	15 (60.0)	24 (75.0)	0.44	0.26
HIV	14 (15.21)	4 (11.4)	5 (20.0)	5 (15.6)	0.73	0.74
TB	4 (4.34)	0	1 (4.0)	3 (9.3)	0.10	0.62
PCT (µg/L), mean (SD)	1.25 (3.63)	1.06 (1.89)	2.52 (6.19)	0.39 (0.60)	0.08	0.78
CRP (mg/L), mean (SD)	204.4 (114.7)	211.8 (127.1)	222.4 (90.9)	181.5 (113.6)	0.23	0.11
Pro-BNP (µg/L), mean (SD)	1 335.3 (3 867.2)	874.2 (1 387.2)	2 416.8 (6 350.4)	948.9 (2 642.7)	0.89	0.27
Trop T (ng/dL), mean (SD)	40.0 (74.4)	51.2 (100.1)	45.7 (63.7)	21.3 (30.4)	0.15	0.09
HbA1c (%), mean (SD)	8.5 (3.0)	8.4 (3.1)	9.5 (3.2)	7.7 (2.6)	0.38	0.06
Mechanical ventilation	57 (62.0)	27 (68.5)	21 (84.0)	9 (28.1)	<0.001	<0.001
Mortality	63 (68.5)	29 (82.9)	22 (88.0)	12 (37.5)	<0.001	<0.001

HAI = hospital-acquired infection; TB = tuberculosis; PCT = procalcitonin; SD = standard deviation; CRP = C-reactive protein; Pro-BNP = pro B-type natriuretic peptide; Trop T = troponin T; HbA1c = glycated haemoglobin.
*Except where otherwise indicated.
†Proven v. none.
‡Suspected v. none.

A sub-analysis was conducted by varying the cut-off values. In patients with PCT levels <0.25 µg/L, the NPV was 92%, whereas PCT levels >1.00 µg/L had a PPV >50%. At PCT levels >1.25 µg/L, sensitivity was lower than specificity, and levels >40 µg/L resulted in a PPV of 100%. This sub-analysis aimed to maximise specificity and minimise sensitivity of the PCT cut-off values.

In patients with suspected biomarkers, the maximum sensitivity and specificity values were 92.0% and 46.0%, respectively. Using a criterion to maximise sensitivity and specificity yielded a maximum sensitivity, but resulted in a lower NPV and PPV of 59.6% and 5.6%, respectively, with an AUC of 0.69 (Fig. 3). Similarly, for CRP, maximum sensitivity and specificity values were 72.0% and 44.6%, respectively, with a resulting lower PPV and NPV of 18.9% and 67.3%, and an AUC of 0.527 (Fig. 4). In patients suspected of having HAI, PCT levels <0.25 µg/L were associated with an NPV >96%, while levels >1.00 µg/L had an NPV >80% and a PPV >39%. At levels >1.47 µg/L, sensitivity was lower than specificity. For PCT levels >40 µg/L, the PPV was 71% (Table 4).

Table 4. Procalcitonin thresholds for different indices in patients with suspected hospital-acquired infection

Threshold (µg/L)	Sensitivity	Specificity	PPV	NPV
0.24	0.96	0.37	0.38	0.96
0.255	0.96	0.38	0.38	0.96
0.93	0.72	0.54	0.38	0.83
1.005	0.72	0.56	0.39	0.83
1.475	0.64	0.65	0.42	0.82
33.02	0.04	0.98	0.50	0.72

PPV = positive predictive value; NPV = negative predictive value.

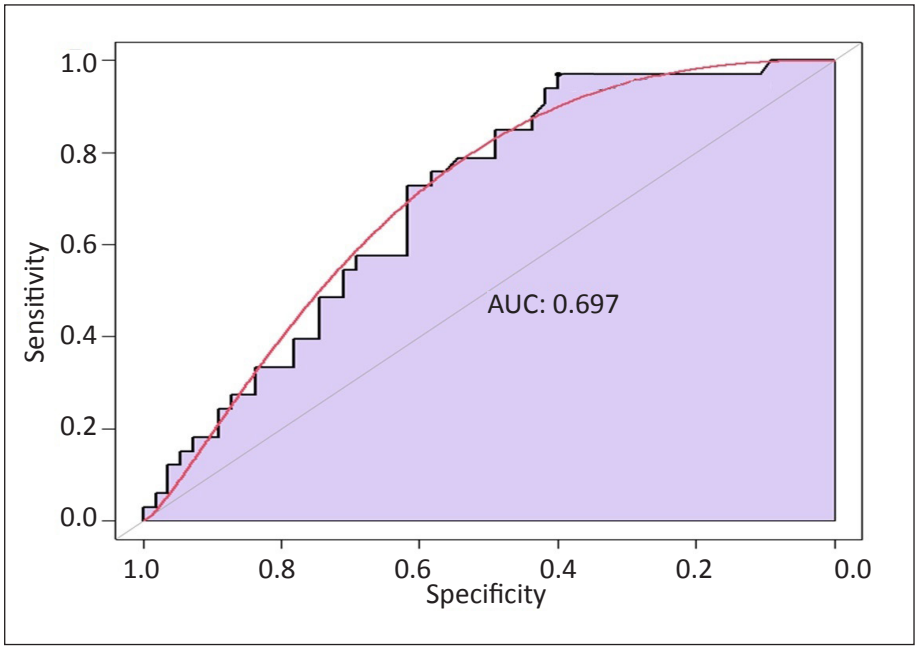

Fig. 1. Receiver operating characteristic curve for procalcitonin in patients with proven hospital-acquired infection. (AUC = area under the curve.)

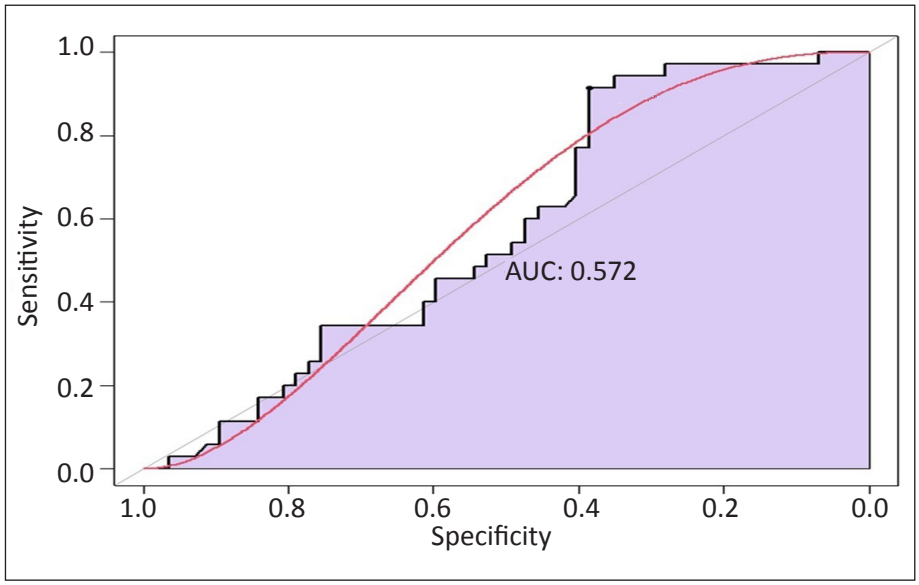

Fig. 2. Receiver operating characteristic curve for C-reactive protein in patients with proven hospital-acquired infection. (AUC = area under the curve.)

Discussion

We found that patients with COVID-19 pneumonia in an ICU, who were admitted without any evidence of secondary sepsis, had high initial CRP levels and low PCT levels. More importantly, our data show that, during an episode of HAI, PCT levels >1.00 µg/L resulted in a moderate PPV of 52%, whereas levels <0.26 µg/L showed a good NPV of 92% for proven HAI. Furthermore, with increased PCT levels, the PPV rose to 100%, making it a better biomarker than CRP, with higher predictive value for predicting HAI in patients with severe COVID-19 pneumonia. CRP values were noted to be consistently elevated and had a poor NPV for HAI.

Van Berkel *et al.*[6] concluded that PCT was a useful biomarker for bacterial sepsis in severe COVID-19. These investigators observed a 93% PPV for PCT levels >1 µg/L and an 81% NPV for levels <0.25 µg/L. They also noted that CRP levels were consistently elevated

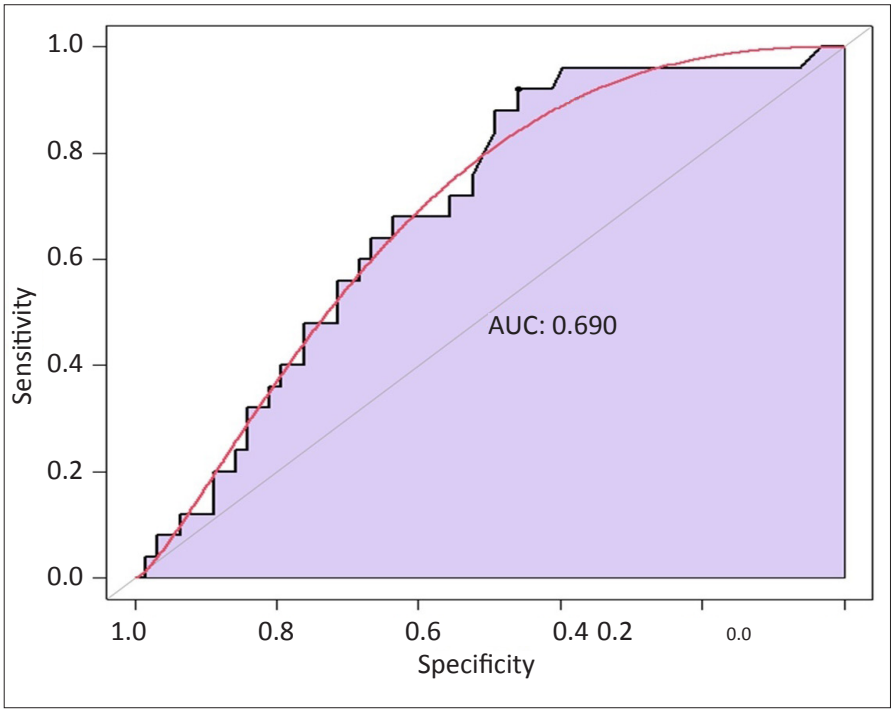

Fig. 3. Receiver operating characteristic curve for procalcitonin in patients with suspected hospital-acquired infection. (AUC = area under the curve.)

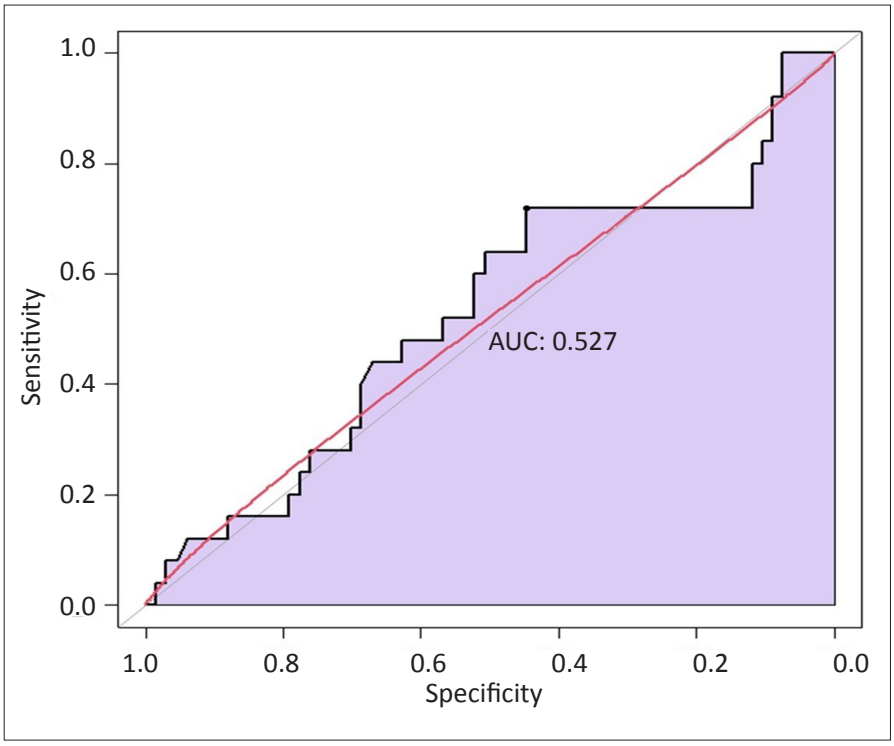

Fig. 4. Receiver operating characteristic curve for C-reactive protein in patients with suspected hospital-acquired infection. (AUC = area under the curve.)

irrespective of bacterial co-infection, and therefore did not support CRP as a biomarker to detect bacterial infection in COVID-19. This conclusion is in keeping with our study findings that CRP serves as a poor biomarker for the detection of bacterial infection. We observed consistently elevated CRP levels irrespective of bacterial co-infections.

The findings of our study concur with the exclusionary utility of PCT observed by Van Berkel *et al.*[6] These investigators also reported that low PCT levels had an NPV of 92% for proven bacterial co-infection. Pink *et al.*[7] observed a similar result in their 2021 study, demonstrating that a PCT level <0.55 µg/L had an NPV of 93% to rule out HAI. In contrast to Van Berkel *et al.*,[6] our findings for the PPV of PCT demonstrated poor clinical utility, with levels between 0.27 µg/L and 1.27 µg/L only able to predict for proven HAI in ~50% of cases of COVID-19. Markedly elevated PCT levels (>40 µg/L) were highly specific for bacterial co-infection in severe COVID-19 pneumonia.

Our findings with regard to the poor PPV of mildly raised PCT for bacterial co-infection have been corroborated in several other studies. Roy *et al.*[8] argued that elevated PCT levels are a marker of disease severity rather than a superadded bacterial infection. This conclusion was supported by their finding that in 101 patients with severe COVID-19 pneumonia, levels >0.25 µg/L were associated with only one blood culture-confirmed case of bacterial co-infection. Similarly, Heer *et al.*[9] demonstrated that increased PCT concentrations were not positively correlated with the prevalence of microbiologically proven sepsis. Elevated PCT levels were, however, associated with the requirement for invasive mechanical ventilation, a marker of disease severity. Garrido *et al.*[10] found that serial PCT values in critically ill COVID-19 patients were not beneficial in detecting HAI and rather served as markers of organ failure. These authors noted an inverse correlation between PCT concentrations and the glomerular filtration rate, postulating that the elevations were due to decreased renal clearance. It therefore appears from their findings that, like CRP, elevated PCT serves more as a marker of disease severity than a biomarker for bacterial co-infection. However, we note that a potential limitation of the studies by Heer *et al.*[9] and Garrido *et al.*[10] is that many of their patients received antimicrobial therapy on their ICU admission, which may have added to the false-negative rate of the microbiological data.

We observed from our results that there is clinical utility for PCT in the context of severe COVID-19 pneumonia. At levels <0.26 µg/L, there was a >90% NPV. This 'rule-out' characteristic of PCT may be especially valuable in scenarios of diagnostic equipoise with regard to the presence of bacterial co-

infection. Clinicians should take care not to unjustifiably associate elevations in PCT levels with the presence of bacterial co-infection, unless levels are extremely high, in which case the PPV rises significantly (100% PPV with levels >40 µg/L). In the absence of a reliable biomarker to predict for bacterial co-infection in severe COVID-19 pneumonia, clinical acumen remains the most valuable tool in the timely treatment of secondary infection and judicious use of antimicrobials.

Our study has certain strengths, including the fact that we were able to access serial PCT and CRP data, which were captured prospectively. A potential weakness is that HAI could only be proven in 35 of the 60 patients suspected of having it. Blood cultures, while highly specific, only have a sensitivity of ~41%, and the false-negative rate may therefore have influenced the results of this study.[11] Furthermore, patients were admitted during various times of the day to the very high-turnover ICU, which may have influenced the comparisons. Moreover, the effect of changes in creatinine clearance on PCT levels was not corrected for in the analysis, and may have impacted on the poor PPV of even significantly raised observed PCT values.

It should be emphasised that the decision to initiate antibiotics was taken by the treating physician(s), and most often not based on a single parameter. We merely report what the value of the PCT could be as an adjunct in the decision to treat (or not treat) a suspected HAI.

Conclusion

During an episode of HAI, PCT levels >1.00 µg/L had a moderate PPV of 52%, whereas levels <0.26 µg/L had an NPV of 92% for proven HAI. Furthermore, with increased PCT values, the PPV rose to 100%, making it a better biomarker than CRP with a higher PPV for HAI.

Data availability. The datasets generated and analysed during the present study are available from the corresponding author (CS) on reasonable request. Any restrictions or additional information regarding data access can be discussed with the corresponding author.

Declaration. The research for this study was done in partial fulfilment of the requirements for CS's MMed (Int) degree at Stellenbosch University.

Acknowledgements. We thank Dr Saadiq Moolla and Dr Caitlin Lyer for assistance with data collection.

Author contributions. The study was conceptualised by CS and CFNK. All authors contributed to data collection. The data were analysed by IF and PSN. The manuscript was written by CS, PSN and CFNK and critically reviewed by all co-authors.

Funding. None.

Conflicts of interest. None.

1. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: A systematic review and meta-analysis. J Infect 2020;81(2):266-275. https://doi.org/10.1016/j.jinf.2020.05.046
2. Moolla MS, Reddy K, Fwemba I, et al. Bacterial infections, antibiotic use and COVID-19: Lessons from the intensive care unit. S Afr Med J 2021;111(6):575-581. https://doi.org/10.7196/SAMJ.2021.v111i6.15590
3. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol 2020;127:104370. https://doi.org/10.1016/j.jcv.2020.104370
4. Cleland DA, Eranki AP. Procalcitonin. Updated 23 April 2023. In: StatPearls (Internet). Treasure Island, Fla.: StatPearls Publishing, January 2024. https://www.ncbi.nlm.nih.gov/books/NBK539794/ (accessed 28 July 2021).
5. Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld ABJ. The diagnostic accuracy of procalcitonin for bacteraemia: A systematic review and meta-analysis. Clin Microbiol Infect 2015;21(5):474-481. https://doi.org/10.1016/j.cmi.2014.12.026
6. Van Berkel M, Kox M, Frenzel T, Schouten J; RCI-COVID-19 study group. Biomarkers for antimicrobial stewardship: A reappraisal in COVID-19 times? Crit Care 2020;24(1):600. https://doi.org/10.1186/s13054-020-03291-w
7. Pink I, Raupach D, Fuge J, et al. C-reactive protein and procalcitonin for antimicrobial stewardship in COVID-19. Infection 2021;49(5):935-943. https://doi.org/10.1007/s15010-021-01615-8
8. Roy A, Powers HR, Craver EC, et al. Antibiotic stewardship: Early discontinuation of antibiotics based on procalcitonin level in COVID-19 pneumonia. J Clin Pharm Ther 2022;47(2):243-247. https://doi.org/10.1111/jcpt.13554
9. Heer RS, Mandal AKJ, Kho J, et al. Elevated procalcitonin concentrations in severe Covid-19 may not reflect bacterial co-infection. Ann Clin Biochem 2021;58(5):520-527. https://doi.org/10.1177/00045632211022380
10. Garrido P, Cueto P, Rovira C, et al. Clinical value of procalcitonin in critically ill patients infected by SARS-CoV-2. Am J Emerg Med 2020;46:525-531. https://doi.org/10.1016/j.ajem.2020.11.011
11. Li Y, Guo J, Yang H, Li H, Shen Y, Zhang D. Comparison of culture-negative and culture-positive sepsis or septic shock: A systematic review and meta-analysis. Crit Care 2021;25(1):167. https://doi.org/10.1186/s13054-021-03592-8

Received 17 October 2023. Accepted 17 October 2024. Published 10 December 2024.