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Evaluation of Procalcitonin's Utility to Predict Concomitant Bacterial Pneumonia in Critically Ill COVID-19 Patients

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Abstract

Background: Historically, procalcitonin(PCT) has been used as a predictor of bacterial infection and to guide antibiotic therapy in hospitalized patients. The purpose of this study was to determine PCT's diagnostic utility in predicting secondary bacterial pneumonia in critically ill patients with severe COVID-19 pneumonia. **Methods:** A retrospective cohort study was conducted in COVID-19 adults admitted to the ICU between March 2020, and March 2021. All included patients had a PCT level within 72 h of presentation and serum creatinine of <1.5mg/dL. A PCT threshold of 0.5ng/mL was used to compare patients with high($\geq$ 0.5ng/mL) versus low(< 0.5ng/mL) PCT. Bacterial pneumonia was defined by positive respiratory culture. A receiver operating characteristics (ROC) curve was utilized to evaluate PCT as a diagnostic test for bacterial pneumonia, with an area under the curve(AUC) threshold of 0.7 to signify an accurate diagnostic test. A multivariable model was constructed to identify variables associated with in-hospital mortality. **Results:** There were 165 patients included: 127 low PCT versus 38 high PCT. There was no significant difference in baseline characteristics, vital signs, severity of disease, or outcomes among low versus high PCT groups (all $p > 0.05$). While there was no difference in bacterial pneumonia in low versus high groups (34(26.8%) versus 12(31.6%), $p = 0.562$), more patients in the high PCT group had bacteremia (19(15%) versus 11(28.9%), $p = 0.050$). Sensitivity was 26.1% and specificity was 78.2% for PCT to predict bacterial pneumonia coinfection in ICU patients with COVID-19 pneumonia. ROC yielded an AUC 0.54 ($p = 0.415$). After adjusting for LDH>350U/L and creatinine in multivariable regression, PCT did not enhance performance of the regression model. **Conclusions:** PCT offers little to no predictive utility in diagnosing concomitant bacterial pneumonia in critically ill patients with COVID-19 nor in predicting increased severity of disease or worse outcomes including mortality.

Keywords

procalcitonin, COVID-19, critical illness, bacterial pneumonia, intensive care unit, SARS-CoV-2

Introduction

In December 2019, the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection emerged in Wuhan, China.[1] As of March 18, 2022, almost 467 million coronavirus disease (COVID-19) cases have been reported worldwide, and over 6 million deaths have occurred since the beginning of the pandemic.[2,3] Although viral pneumonia is common in COVID-19 patients with severe disease, distinguishing secondary concomitant bacterial pneumonia from viral COVID-19 pneumonia is difficult, even when using chest radiographs and computerized tomography imaging alone.[2,4] This can lead to a delay in diagnosing bacterial infections and often results in antibiotic overuse for presumed bacterial pneumonia, which may contribute to the development of antibiotic resistance, *Clostridium difficile* infection, drug toxicities, mortality, and increased costs.[5–7] Procalcitonin (PCT) has been lauded as a useful diagnostic and prognostic biomarker and is often cited in hospital algorithms to guide antibiotic therapy for lower respiratory tract infections. PCT a 116 amino acid peptide precursor of calcitonin, is typically found at concentrations of 0.1 ng/mL or less in healthy individuals.[8] PCT is produced in the C-cells of the thyroid gland and increases within 4 to 12 h in the presence of bacteria or bacterial endotoxin.[5,7,9] The release of PCT is enhanced by tumor

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necrosis factor and interleukin-6, cytokines typically seen in bacterial infections, but attenuated by interferons, which are usually elevated during viral infections.[5,9]

In COVID-19, PCT has been investigated as a biomarker to distinguish between viral pneumonia and concomitant bacterial infections. Conflicting evidence exists regarding the utility of procalcitonin in diagnosing bacterial coinfections.[10–14] PCT has been investigated as a tool to diagnose ventilator-associated pneumonia (VAP)[15] and secondary pulmonary infections, including both viral and bacterial infections, in patients with COVID-19.[16,17] Although early literature suggests that elevated PCT is associated with COVID-19 disease severity and increased mortality, there is a paucity of data specific to critically ill COVID-19 patients with concomitant bacterial pneumonia.[10,11,18–20] The role of PCT in distinguishing between viral and bacterial pneumonia in COVID-19 patients remains unclear. The purpose of this study was to determine the utility of PCT in predicting secondary bacterial pneumonia coinfection in critically ill patients with COVID-19. We hypothesized that high PCT does not predict bacterial pneumonia in patients with severe COVID-19.

Methods

Study Design

A single-center retrospective cohort study was conducted at a 355-bed community hospital in New Jersey. Patients 18 years of age and older presenting to the hospital between March 11, 2020, and March 11, 2021, who required admission to the intensive care unit (ICU) for COVID-19 were assessed for eligibility. Inclusion criteria included a positive nasopharyngeal swab reverse transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 and a PCT level within 72 h of hospital presentation. Patients with a baseline serum creatinine of 1.5 mg/dL or greater were excluded as prior literature identified PCT was inversely related to glomerular filtration rate and therefore PCT's value cannot be assured in patients with poor renal function.[10]

The electronic medical record system, Allscripts Sunrise Clinical Manager (Chicago, IL) was used to abstract data. Collected variables were defined, a standardized data abstract form was utilized, and abstractors were trained on the utilization of the form prior to assembling data. Abstractors were not blinded to patient assignment and abstractors' performance was verified by the principal investigator. Data collected included demographics, comorbidities, vital signs, laboratory tests, complications, and outcomes including ventilator days, length of hospital and ICU stays, and mortality.

Low PCT was defined as <0.5 ng/mL, whereas high PCT was defined as ≥ 0.5 ng/mL based on previous literature.[5,21,22] Bacterial pneumonia was defined as a positive respiratory culture from sputum, endotracheal suction aspirate or bronchoalveolar lavage fluid. Timing of respiratory cultures was based on physician discretion if concomitant bacterial pneumonia was clinically suspected. Complications to determine severity of disease included septic shock requiring vasopressors, acute respiratory distress syndrome (ARDS) defined by the Berlin criteria, and acute kidney injury as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) definition.

The study's primary endpoint was to determine the diagnostic utility of PCT in identifying bacterial pneumonia coinfection in critically ill patients with COVID-19 viral pneumonia. Secondary aims included comparing characteristics, complications, and outcomes among patients with low versus high PCT, and to determine if elevated PCT was associated with increased severity of disease, poor outcomes, and worse in-hospital mortality.

Statistical Analyses

The sensitivity and specificity of PCT in predicting concomitant bacterial pneumonia were calculated using a cut-off of ≥ 0.5 ng/mL. Categorical and continuous variables were analyzed using the Pearson chi-square test (or Fisher's exact test) and Student's t-test, respectively. Data were reported using proportions for categorical variables and mean plus standard deviation for continuous variables unless they were non-normally distributed. The normality of the data was assessed by visual inspection of histogram plots and the Kolmogorov–Smirnov test. Non-normally distributed data were reported using the median and interquartile range and analyzed using the Mann-Whitney U test. The threshold for missing data was <10% and handled using multiple imputation. A receiver operating characteristics (ROC) curve was created to assess the diagnostic utility of PCT in predicting secondary bacterial coinfection in critically ill patients with COVID-19, the area under the ROC curve (AUC) threshold of 0.7 was required to meet the minimal "acceptable" threshold for a diagnostic test.[23]

Multivariable logistic regression using mortality as the dependent outcome was constructed to identify variables associated with death. Covariates were selected based on $p < 0.2$ in univariate analyses and/or a prior knowledge of confounding then entered stepwise in the multivariable regression. Only covariates with a $p < 0.05$ in the final model were retained. Overall model fit was evaluated using the Hosmer-Lemeshow goodness of fit test. All analyses were performed as 2-sided tests, and a p-value of ≤0.05 was considered significant. All data were analyzed using SPSS version 27 (IBM Corporation, Armonk, NY).

Results

There were 258 patients admitted to the ICU with COVID-19 during the study period. Of the 258 patients, 36 were excluded because they lacked a PCT level within 72 h of presentation, an additional 56 were excluded due to a baseline serum creatine of 1.5 mg/dL or greater, and one was excluded as he was transferred during his hospital course (Figure 1). Therefore, a total of 165 patients were included in the final analysis. Of these patients, 127 had a low PCT and 38 had a high PCT on admission (Table 1). The mean age of all COVID-19 ICU patients was 63.3 years, 66.1% were male, and 29.1%

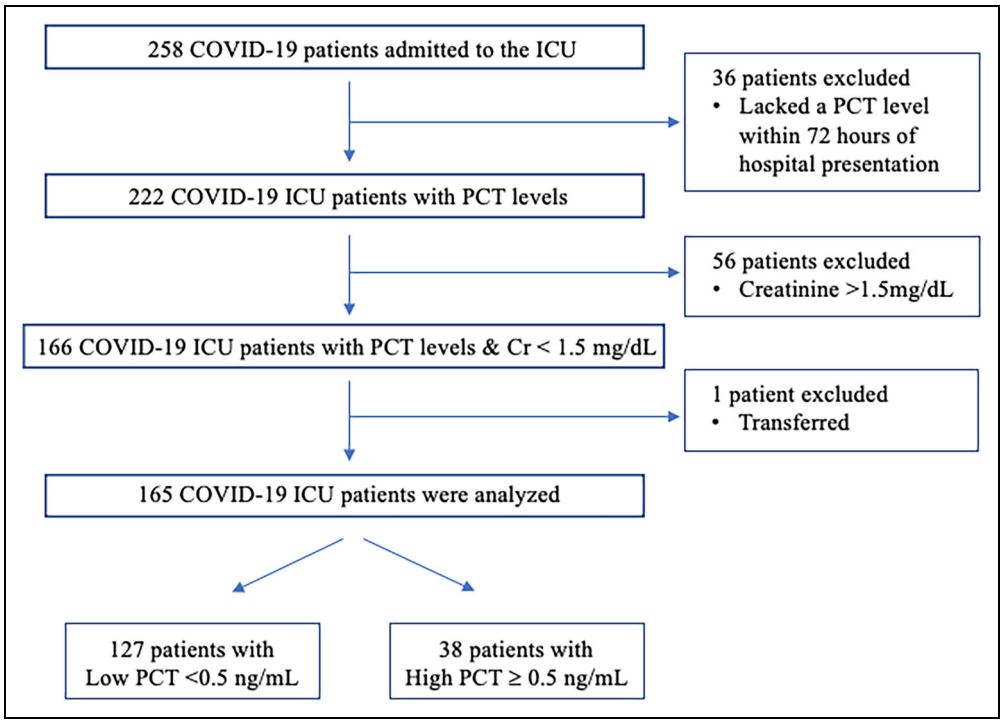

Figure 1. Prisma flow diagram for the study.

Table 1. Baseline Characteristics and Comorbidities of Critically Ill Patients with COVID-19 Stratified by Procalcitonin Level.

	All COVID-19 ICU Patients (N = 165)	COVID-19 ICU Patients with PCT <0.5 (n = 127)	COVID-19 ICU Patients with PCT ≥0.5 (n = 38)	p-value
Age, years (Mean ± SD)	63.60 ± 13.84	63.68 ± 14.03	63.34 ± 13.37	0.896
Sex, male (n, %)	109 (66.1)	82 (64.6)	27 (71.1)	0.459
Race/Ethnicity				
Caucasian	79 (50)	64 (52.9)	15 (40.5)	0.189
Black	12 (7.6)	8 (6.6)	4 (10.8)	0.478
Hispanic	46 (29.1)	32 (26.4)	14 (37.8)	0.182
Asian	21 (13.3)	17 (14.0)	4 (10.8)	0.784
Comorbidities				
Chronic Obstructive Pulmonary Disease	18 (11.0)	15 (11.9)	3 (7.9)	0.767
Obstructive Sleep Apnea	13 (7.9)	11 (8.7)	2 (5.3)	0.774
Diabetes	60 (36.4)	46 (36.2)	14 (36.8)	0.938
Hypertension	97 (58.8)	78 (61.4)	19 (50.0)	0.218
Heart Failure	13 (7.9)	11 (8.7)	2 (5.3)	0.774
Coronary Artery Disease	23 (13.9)	18 (14.2)	5 (13.2)	0.904
Chronic Kidney Disease	4 (2.4)	2 (1.6)	2 (5.3)	0.455
Obesity – Body Mass Index (Mean ± SD)	31.86 ± 7.19	31.98 ± 6.82	31.46 ± 8.39	0.696

Abbreviations: SD, standard deviation.

were Hispanic. There was no significant difference in baseline characteristics, comorbidities, or vital signs between those patients with low versus high PCT as summarized in Tables 1 and 2 (all $p > 0.05$). Patients in the high PCT cohort had a greater mean white blood cell count (10.9×10^9/L ± 5.41 vs. 7.8 ± 3.5, $p = 0.002$) and creatinine level (1.02mg/dL ± 0.27 vs. 0.87 ± 0.27, $p = 0.003$).

Treatments, complications, and outcomes of the patients are depicted in Table 3. There was no difference in remdesivir, tocilizumab, or corticosteroid treatments among the high versus low PCT groups (all $p > 0.05$, Table 3). Critical illness was common with 89.7% of all patients having ARDS, 60% requiring vasopressors for septic shock, and 45.5% having acute kidney injury; there was no statistical difference noted in

Table 2. Vital Signs and Laboratory Results of Critically Ill Patients with COVID-19 Stratified by Procalcitonin Level.

	All COVID-19 ICU Patients (N = 165)	COVID-19 ICU Patients with PCT <0.5 (n = 127)	COVID-19 ICU Patients with PCT ≥0.5 (n = 38)	p-value
Admission Vital Signs (Mean ± SD)				
Temperature, degrees Fahrenheit	99.93 ± 1.88	99.86 ± 1.84	100.15 ± 2.02	0.408
Heart Rate, beats per minute	100.90 ± 17.78	99.74 ± 16.84	104.79 ± 20.37	0.125
Systolic Blood Pressure, mm Hg	134.59 ± 23.81	134.10 ± 22.23	136.21 ± 28.75	0.634
Mean Arterial Pressure	93.77 ± 15.08	93.68 ± 14.61	94.05 ± 16.77	0.895
Initial O_2 Saturation	86.42 ± 14.32	87.07 ± 14.54	84.19 ± 13.51	0.283
Admission Laboratory Results				
White Blood Cell Count, x10^9/L	8.51 ± 4.21	7.80 ± 3.50	10.89 ± 5.41	0.002
Creatinine, mg/dL	0.90 ± 0.28	0.87 ± 0.27	1.02 ± 0.27	0.003
Lactate Dehydrogenase	770.0 ± 1422.4	812.2 ± 1608.5	623.5 ± 231.8	0.485

Abbreviations: SD, standard deviation.

Table 3. Treatments, Complications, and Outcomes of COVID-19 ICU Patients Stratified by Procalcitonin Level.

	All COVID-19 ICU Patients (N = 165)	COVID-19 ICU Patients with PCT <0.5 (n = 127)	COVID-19 ICU Patients with PCT ≥0.5 (n = 38)	p-value
Remdesivir (n, %)	80 (48.5)	62 (48.8)	18 (47.4)	0.875
Tocilizumab	56 (33.9)	45 (35.4)	11 (28.9)	0.459
Steroids	100 (60.6)	75 (59.1)	25 (65.8)	0.456
ARDS	148 (89.7)	113 (89.0)	35 (92.1)	0.616
Severe ARDS	113 (68.5)	84 (66.1)	29 (76.3)	0.243
Chemical Neuromuscular Blockade	56 (33.9)	41 (32.2)	15 (39.5)	0.467
Prone Positioning	91 (55.2)	71 (55.9)	20 (52.6)	0.722
Septic Shock Requiring Vasopressor	99 (60.0)	73 (57.4)	26 (68.4)	0.193
Infectious Complications				
Bacterial Pneumonia	46 (27.9)	34 (26.8)	12 (31.6)	0.562
Urinary Tract Infection	19 (11.5)	13 (10.2)	6 (15.8)	0.347
Bacteremia	30 (18.2)	19 (15.0)	11 (28.9)	0.050
Acute Kidney Injury	75 (45.5)	54 (42.5)	21 (55.3)	0.191
Renal Replacement Therapy	31 (18.8)	20 (15.7)	11 (28.9)	0.075
Deep Vein Thrombosis	6 (3.6)	4 (3.1)	2 (5.3)	0.622
Pulmonary Embolism	9 (5.5)	7 (5.7)	2 (5.3)	1.000
Arrhythmia	39 (23.8)	30 (23.8)	9 (23.7)	0.987
Myocardial Infarction	10 (6.2)	7 (5.5)	3 (7.9)	0.701
Cardiomyopathy	6 (3.6)	4 (3.1)	2 (5.3)	0.622
Ventilator Days, median (IQR), days	11 (6.0 – 18.0)	11 (6.0 – 18.3)	10 (6.5 – 18.5)	0.970
ICU Length of Stay, days	9 (5.0 – 18.0)	9 (5.0 – 18.0)	9.5 (5.0 – 22.0)	0.887
Hospital Length of Stay, days	16 (11.0 – 25.5)	16 (11.0 – 25.0)	16 (9.0 – 27.5)	0.797
Mortality (n, %)	79 (47.9)	57 (44.9)	22 (57.9)	0.159

Abbreviations: ICU, intensive care unit; IQR, Interquartile Range; ARDS, acute respiratory distress syndrome.

these variables depicting severity of illness when comparing high versus low PCT groups (all $p > 0.05$, Table 3).

When comparing infectious complications, there was no statistical difference in patients in the low versus high PCT group who developed bacterial pneumonia (34 (26.8%) versus 12 (31.6%), $p = 0.56$) or urinary tract infections (13 (10.2%) versus 6 (15.8%), $p = 0.35$). However, more patients in the high PCT group developed bacteremia (19 (15%) versus 11 (28.9%), $p = 0.05$). When comparing other complications, there was no significant difference among the two groups. Likewise there was no difference when comparing outcomes including ventilator days (11 days (IQR 6-18.3) versus 10 (6.5-18.5), $p = 0.97$), ICU length of stay (9 days (5-18) versus 9.5 (5-22), $p = 0.89$), hospital length of stay (16 days (11-25) versus 16 (9-27.5), $p = 0.80$), or mortality (57 (44.9%) versus 22 (57.9%), $p = 0.16$).

When using a PCT threshold of ≥ 0.5 ng/mL, the sensitivity and specificity of PCT in predicting superimposed bacterial pneumonia was to 26.1% (95% CI: 14.3-41.1) and 78.2% (95% CI: 69.7-85.2), respectively, as shown in Table 4. The positive and negative predictive values were 31.6% (95% CI: 20.3-45.5) and 73.2% (95% CI: 69.2-76.9), respectively. The ROC curve depicted in Figure 2 yielded an AUC of 0.54 ($p = 0.451$) and did not support the diagnostic utility of PCT to

Table 4. Utility of Procalcitonin in Detecting Bacterial Co-Infection in COVID-19 ICU Patients.

Sensitivity	26.09% (95% CI: 14.27 – 41.13)
Specificity	78.15% (69.65 – 85.20)
Positive Predictive Value	31.58% (20.32 – 45.52)
Negative Predictive Value	73.23% (69.21 – 76.90)

Abbreviations: PCT, procalcitonin.
Reference range: Low PCT <0.5 ng/mL. High PCT ≥ 0.5 ng/mL.

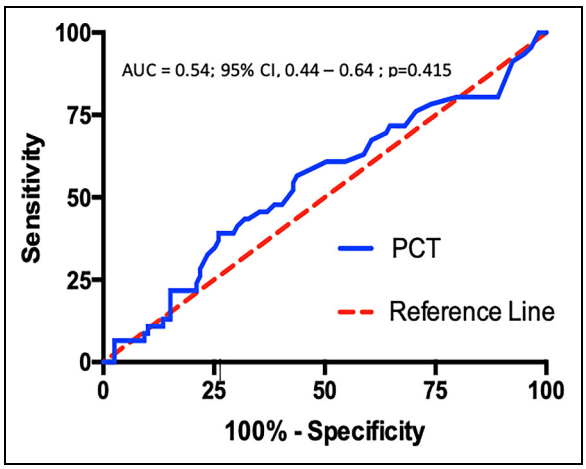

Figure 2. Procalcitonin (PCT) receiver operating characteristics curve for bacterial pneumonia. The figure demonstrates that PCT has little value in a bacterial pneumonia diagnostic test in critically ill patients with COVID-19.

identify concomitant bacterial pneumonia infection in critically ill patients with COVID-19.

When using mortality as the dependent outcome to identify variables associated with COVID-19 and death in a multivariate regression analysis after adjusting for LDH > 350 U/L and serum creatinine, PCT was not found to be associated with mortality (Table 5). The equation describing the regression is provided below:

$$\text{logit}(\text{in} - \text{hospital mortality}|\text{male sex},\ \text{LDH} > 350\,\text{U/L},\ \times \text{serum creatinine} = \beta_0 + \beta_1 \times \text{male sex} + \beta_2 \times \text{LDH} > 350\,\text{U/L} + \beta_3 \times \text{serum creatinine}$$

Discussion

The results of our study demonstrate that PCT ≥ 0.5 ng/mL within 72 h of hospital presentation does not predict concomitant bacterial pneumonia in critically ill patients with COVID-19. With an AUC of 0.54, our data fail to reach the threshold of 0.7 required to meet the minimal "acceptable" level for diagnostic accuracy.[23]

Previous studies have demonstrated that although PCT is not a reliable indicator of the *presence* of concomitant bacterial pneumonia in COVID-19 patients, its absence is assured with a negative predictive value (NPV) of 91.7% or higher.[13,14] This was not demonstrated in our critically ill population, where NPV was only 73.2%. Prior research in this area has

Table 5. Multivariable Analysis of Variables Associated with Mortality in Critically Ill Patients with COVID-19.

	β	SE	95% CI	p value
Sex, Male	0.433	0.365	0.2.12–0.885	0.022
LDH > 350 U/L	3.809	0.609	1.154–12.578	0.028
Creatinine, 1 mg/dL unit increase	5.693	1.739	1.564–20.718	0.008
Constant	0.078	0.797		0.001

*After adjusting for LDH>350 U/L and creatinine.
Abbreviations: CI, Confidence Interval.

not targeted ICU patients with COVID-19, likely accounting for the discrepant predictivity of PCT. This is not the first viral pneumonia pandemic in which the utility of PCT was assessed. PCT was implicated as a useful diagnostic marker for bacterial coinfections during the influenza A (H1N1) virus pandemic, and similar to our findings, multiple studies concluded that PCT correlated with poor sensitivity and NPV for detecting concomitant bacterial pneumonia in ICU patients.[24–28] Using PCT to rule out a diagnosis of bacterial pneumonia in critically ill COVID-19 patients is potentially dangerous and may result in delayed initiation of antibiotics and increased morbidity or mortality

Along with PCT's lack of predictive ability, there is no consensus as to its threshold for clinical significance. Multiple studies have evaluated PCT's ability to diagnose bacterial infections and guide antibiotic therapy, particularly in the setting of lower respiratory tract illnesses and sepsis.[6,7,9,21,29] Cutoff values of 0.1, 0.25, and 0.5 ng/mL have been used in high quality studies to assess the correlation between PCT and bacterial PNA.[5,14,22]

Procalcitonin may not have much utility for predicting bacterial coinfection, however some suggest it serves as a prognostic biomarker. Vanhomwegan and colleagues found a positive correlation between PCT levels and mortality in an ICU in Belgium.[11] Similar results were demonstrated by Dolci, et al They found that a PCT of greater than 6.7 ug/L had moderate strength in predicting in-hospital death, but did not add value as a diagnostic or prognostic biomarker compared to other more common markers of infection such as blood lymphocyte percentage and neutrophil count.[14]

It has been suggested that elevated PCT may be a marker of the cytokine storm caused by the SARS-CoV-2 virus versus bacterial pneumonia. The cytokine storm is a hyperactive response of the immune system to the SARS-CoV-2 virus, resulting in the release of large amounts of pro-inflammatory cytokines such as IL-6, IL-10, and TNF-*a*. IL-6 is a particularly notable known of cause PCT elevations.[30] This hyper-inflammation and cytokine storm caused by COVID-19, ultimately decreases the discriminatory power of PCT.[12]

Additionally, due to increased pro-inflammatory metabolites, approximately 36% of patients with chronic kidney disease have baseline PCT of 0.5 ng/mL or greater.[31] In fact,

PCT has been shown to be inversely related to glomerular filtration rate in critically ill COVID-19 patients.[10] Based on these findings and the lack of definitive guidance regarding PCT and renal function, a total of 56 patients were excluded from the analysis due to a baseline serum creatinine of 1.5 mg/dL or greater. This suggests that a large portion of PCT levels may be subject to inappropriate interpretation. While all patients included in the study had an initial creatinine <1.5mg/dL on presentation, 45.5% of those patients went on to develop acute kidney injury after 72 h of admission during their ICU course, therefore we do not believe the utility of PCT would improve if measured beyond 72 h of presentation in this patient population.

The literature has suggested several predictors of mortality. For example, although not found to be significant in our study, fever has previously been described as a predictor of mortality in critically ill COVID-19 patients requiring mechanical ventilation.[32] Additionally, Bhatt and colleagues found that patients with severe COVID-19 and secondary bloodstream infections had higher mean baseline white blood cell count and creatinine.[4] Despite limited diagnostic or prognostic utility of PCT in our patients, we found that those in the high PCT cohort were more likely to experience bacteremia, have higher baseline white blood cell count, and higher creatinine than those in the low PCT group. This may all be evidence indicative of the systemic inflammation caused by COVID-19.[4]

Limitations of this study include that it was a retrospective, single-center study with a small sample size, therefore limiting our ability to use sample size calculation. Additionally, PCT levels were ordered based on the discretion of the physicians, which may have led to selection bias. Moreover, some patients may have had a concomitant bacterial infection, but cultures may not have been ordered, or they may have failed to detect the presence of bacterial pathogens. Conversely, since bacterial pneumonia was defined by positive respiratory cultures, specimens with colonization could have been included therefore overestimating the sample size. Hospital day of admission to the ICU also varied per patient, so the PCT test's timing to critical illness was not standardized. A future prospective, randomized controlled multicenter trial would provide a standardized approach to further evaluate the utility of procalcitonin.

Conclusion

Our study revealed there is little to no predictive utility of PCT in diagnosing concomitant bacterial pneumonia in critically ill patients with COVID-19. Elevated PCT within 72 h of hospital presentation did not predict bacterial pneumonia coinfection in COVID-19 ICU patients nor did it predict a difference in severity of disease or outcomes such as hospital length of stay, ICU length of stay, ventilator days, or mortality.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

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