Procalcitonin and COVID-19: A Reliable Clinical Tool

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Abstract

BACKGROUND: A procalcitonin (PCT) level is commonly ordered to distinguish between bacterial and viral etiologies of lower respiratory tract infections as it is typically negative in the absence of inflammatory conditions and bacterial infections. With COVID-19 causing an influx of patients presenting with respiratory symptoms, clinicians are in need of useful tools to guide management of these patients. Given the inflammation that is caused by COVID-19, it is currently unknown whether PCT continues to be a reliable or useful test in suspected and confirmed cases of COVID-19 pneumonia.

OBJECTIVE: To determine whether PCT remains a clinically useful test in patients who present with lower respiratory tract symptoms in the era of COVID-19.

DESIGN: Single-center retrospective cohort study

PARTICIPANTS: 243 adults with lower respiratory tract symptoms who presented to the hospital through the emergency department between April 11, 2020 and May 18, 2020 who received both a COVID-19 test as well as a PCT level.

MAIN MEASURES: COVID-19 positivity/negative, PCT level

KEY RESULTS: It was found that patients with COVID-19 consistently had negative procalcitonin levels ($<0.25\text{ng/mL}$). Based on the odds ratio, a patient with a positive PCT level was 3.4 times more likely to test negative for COVID than a patient with a PCT level $<0.25\text{ng/mL}$.

(1)=13.895, $p<0.001$.

CONCLUSIONS: There is a highly significant association between a negative procalcitonin and positive COVID-19 infection, thus supporting the continued use of PCT in the COVID-19 era.

Introduction

Procalcitonin (PCT), a precursor of calcitonin, was first noted to be elevated in 1993 in patients with sepsis and infection. It then emerged as a biomarker distinguishing between infectious and non-

infectious causes of inflammatory states, as it is typically negative in the general population [1]. Its production is linked to bacterial endotoxins as well as inflammatory cytokines such as TNF, IL-1B, and IL-6 [2]. This allows for its use predicting whether respiratory infections are of bacterial or viral etiology. A large multicentric study in 1,735 patients with community-acquired pneumonia (CAP) demonstrated PCT's ability to discriminate between bacterial and viral infections with approximately 70% accuracy. A PCT threshold of 0.1ng/mL resulted in 80.9% (95% CI, 75.3%-85.7%) sensitivity and 51.6% (95% CI, 46.6%-56.5%) specificity for identification of any bacterial pathogen [3]. This has led to the test being widely ordered by clinicians for the purpose of initiation and discontinuation of antibiotics in patients presenting with symptoms of lower respiratory tract involvement such as fever, cough, dyspnea, fatigue, sputum production, and myalgia.

Little is known about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as it relates to PCT. One of the ways in which this virus can act is by triggering an inflammatory cascade via release of pro-inflammatory cytokines such as IL-1B and IL-6—two of the inflammatory cytokines also known to trigger PCT release [2]. Given the known inflammatory aspects of SARS-CoV-2, this study aims to observe whether PCT remains a clinically useful test in patients who present with lower respiratory symptoms in the era of COVID-19.

Methods

This is a single-center retrospective cohort study. Charts were reviewed on patients who met the outlined criteria between April 11, 2020 and May 18, 2020. COVID-19 status, as determined by the BioFire rapid PCR testing, as well as PCT levels were recorded. All methods were approved by the NCH Healthcare System IRB committee and performed in accordance with HIPAA requirements. Informed consent was waived as this study was conducted retrospectively and there was no storage of protected health information. Both the COVID-19 testing and PCT testing were performed as determined appropriate per the standards of care and the treating physician. A total of 243 patients' test results were used for analysis based on the set inclusion and exclusion criteria.

Inclusion criteria was as follows: males and females over the age of 18 years who presented to the hospital and met the criteria for COVID-19 testing set forth by the CDC and Department of Health and who had a documented PCT result during hospitalization. Those excluded included: patients under 18, trauma patients, burn patients, those with end-stage renal disease (ESRD), intracranial hemorrhage, or pancreatitis (chronic or acute). Vulnerable populations including children, pregnant women, fetuses, neonates, or prisoners were not included.

Ordering of PCT and COVID-19 rapid PCR was performed by attending physicians and staff in the emergency department/hospital. Lab tests were run by Naples Community Hospital laboratory personnel and were standardized across all patients. All records of data collection were stripped of patient identifiers and stored in a HIPAA-compliant environment.

The assay used to measure PCT was the VIDAS B.R.A.H.M.S PCT assay—a one-step immunoassay sandwich method with a final fluorescent detection (enzyme-linked fluorescent assay) with sensitivity of 0.9 and a specificity of 0.31 (cut off 0.23ng/ml) with a coefficient of variation 3.9%-7.1% at a mean concentration of 0.23-92.3ng/ml [4]. COVID-19 testing was performed using the BioFire COVID-19 test—a nested multiplexed real-time RT-PCR test intended for the qualitative detection of nucleic acid from SARS-CoV-2 in nasopharyngeal swabs in transport media from individuals suspected to have COVID-19. This test has a positive percent agreement and a negative percent agreement each of 100% with a limit of detection of 3.3E+02 GC/mL (2.2E-02 TCID50/mL), [5].

Patients were categorized into one of four groups: Group 1: COVID-19 (+) PCT (+), Group 2: COVID-19 (+) PCT (-), Group 3: COVID-19 (-) PCT (+) and Group 4: COVID-19 (-) PCT (-). For the purposes of this study, a PCT level of 0.25ng/mL or greater was considered positive. Frequencies were calculated and shown in a crosstabulation table. Pearson’s chi-squared analysis was used for comparison between the PCT level and COVID-19 test result, and an odds ratio was calculated.

Results

Out of the 243 patients analyzed, 150 tested positive for SARS-CoV-2 and 93 tested negative. Of those patients who tested negative for COVID-19, 37.3% had a positive PCT level and 62.7% had a negative PCT level. Of those who were positive for the disease, 15.1% had positive PCT levels and 84.9% had negative PCT levels as demonstrated in Table 1.

Table 1

		In-house COVID-19 result		Total
		NEG	POS	
PCT≥ .25ng/mL	Count	56	14	70
	0.25 – 2ng/mL	22.6%	8.6%	
	>2ng/mL	14.7%	6.5%	
	Total % within in-house COVID result	37.3%	15.1%	28.8%
PCT< .25ng/mL	Count	94	79	173
	0 – 0.15ng/mL	57.4%	67.7%	
	0.16 – 0.24ng/mL	5.3%	17.2%	
	Total % within in-house COVID result	62.7%	84.9%	71.2%
Total	Count	150	93	243

Table 1. Procalcitonin level ranges of patients testing either positive or negative for COVID-19.

Pearson's chi-squared analysis demonstrates that a significant association exists between PCT level and detection of SARS-CoV-2 (χ^2 (1)=13.895, $p<0.001$). Based on the odds ratio, a negative COVID-19 test result and PCT level greater than or equal to 0.25ng/mL is 3.4 times more likely than a positive COVID-19 test result and PCT level greater than or equal to 0.25ng/mL.

Discussion And Conclusion

The PCT level was measured on 243 patients who met the inclusion criteria, out of which 150 patients tested negative for COVID-19 and 93 patients were found to be positive. 84.9% of COVID-19 patients had negative procalcitonin levels (<0.25ng/ml). Of those, 67.7% had a procalcitonin level between 0 and 0.15ng/mL. In the absence of conditions which could potentially artificially raise PCT levels such as ESRD, trauma, burns, intra-cranial hemorrhage, and pancreatitis, PCT levels in COVID-19 patients were persistently negative despite a broad spectrum of disease severity. Based on the calculated odds ratio, a patient who presents with lower respiratory symptoms and a PCT level greater than or equal to 0.25ng/mL is 3.4 times less likely to also have COVID-19 ($p<0.001$). This indicates that despite the known inflammation caused by COVID-19, the low PCT with SARS-CoV-2 demonstrated here is consistent with the PCT levels in other viral respiratory infections. Moreover, the positive PCT level cut off of 0.25ng/ml used here is even lower than that of 0.5ng/ml in the existing literature on this subject [6]. This finding is supported by one other study in the literature which analyzed characteristics of patients with COVID-19 and demonstrated that they have lower levels of plasma PCT (<0.5ng/mL) [7]. The consistently low PCT level in these patients paired with the lowered cutoff for procalcitonin positivity suggests that serum PCT in patients with lower respiratory symptoms cases remains a quick and readily available tool in the era of COVID-19. It could also, therefore, potentially be used to guide clinicians in antibiotic initiation and discontinuation without increasing mortality or treatment failure [8, 9].

Despite the highly significant relationship between PCT and COVID-19, there were still 14 COVID-19 patients who had elevated PCT >0.25. Out of those 14 patients, 7 of them required ICU level of care due to increasing oxygen requirements and need for non-invasive positive pressure ventilation. Two patients demonstrated evidence of cytokine storm, and 3 of these patients died of hypoxemic respiratory failure. The most plausible explanation of an elevated PCT level in COVID-19 patients would be bacterial co-infection [1]. Interestingly, blood cultures, MRSA and legionella screen in all these patients were negative. One possibility for the rise in PCT with absence of obvious infection could be due to the severe inflammation and release of pro-inflammatory cytokines such as IL-1B and IL-6—two of the inflammatory cytokines also known to trigger PCT release [2]. A recent study of 140 Covid-19 patients noted PCT level to be increased in 25% of positive patients admitted to the ICU compared with 0% in patients who were not ($p=0.029$) [10]. This could support the use of PCT as a biomarker for severe COVID-19, particularly in those patients without evidence of co-infection. However, additional studies looking specifically at this patient population are needed before any such statement can be made with statistical significance.

In conclusion, despite its inflammatory effects, SARS-CoV-2 does not significantly elevate the procalcitonin level above 0.25. These findings support the continued use of PCT as a clinical tool in the COVID-19 era.

Declarations

- This study involved human subjects.
- The author confirmed that all appropriate ethical guidelines for the use of human subjects have been followed, any necessary IRB and/or ethics committee review has been obtained, and information about the IRB/ethics committee is included in the manuscript.
- The author has confirmed that all necessary patient/participant consent or assent has been obtained and the appropriate institutional forms have been archived. If the IRB/ethics committee waived the requirement for patient/participant consent or assent, an explanation for the waiver is included in the text.
- The author has confirmed that a statement listing potential conflicts of interest or lack thereof is included in the text.

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