Clinical Studies

Elucidating the role of procalcitonin as a biomarker in hospitalized COVID-19 patients

Kelsie Cowman[a,e,*], James Rossi[a], Inessa Gendlina[a], Yi Guo[b], Sichen Liu[c], Wendy Szymczak[d], Stefanie K. Forest[d], Lucia Wolgast[d], Erika Orner[d], Hongkai Bao[b], Miguel E. Cervera-Hernandez[a], Ashley Ceniceros[a], Raja Thota[e], Liise-anne Pirofski[a,f], Priya Nori[a]

[a] Division of Infectious Diseases, Department of Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA
[b] Department of Pharmacy, Montefiore Medical Center, Bronx, NY, USA
[c] Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA
[d] Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA
[e] Network Performance Group, Montefiore Medical Center, Bronx, NY, USA
[f] Department of Microbiology and Immunology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, USA

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ABSTRACT

Our objectives were to evaluate the role of procalcitonin in identifying bacterial co-infections in hospitalized COVID-19 patients and quantify antibiotic prescribing during the 2020 pandemic surge. Hospitalized COVID-19 patients with both a procalcitonin test and blood or respiratory culture sent on admission were included in this retrospective study. Confirmed co-infection was determined by an infectious diseases specialist. In total, 819 patients were included; 335 (41%) had an elevated procalcitonin (>0.5 ng/mL) and of these, 42 (13%) had an initial bacterial co-infection. Positive predictive value of elevated procalcitonin for co-infection was 13% while the negative predictive value was 94%. Ninety-six percent of patients with an elevated procalcitonin received antibiotics (median 6 days of therapy), compared to 82% with low procalcitonin (median 4 days of therapy) (adjusted OR:3.3, $P < 0.001$). We observed elevated initial procalcitonin in many COVID patients without concurrent bacterial co-infections which potentially contributed to antibiotic over-prescribing.

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1. Introduction

Widespread use of empiric antibiotics in hospitalized COVID-19 patients was universally observed during the first COVID-19 pandemic surge despite low rates of confirmed bacterial coinfection [1]. A retrospective study from our medical center indicated that 71% of admitted COVID-19 patients received antibiotics despite only 3.6% having a confirmed bloodstream or respiratory coinfection [2]. Likewise, a meta-analysis reported that up to 72% of COVID-19 patients received broad spectrum antibiotics, while 8% had a confirmed coinfection [3]. One study reported community-onset bacterial co-infections in only 3.5% of all patients in their multicenter analysis [4]. Moreover, 21.2% of patients without a community-onset bacterial co-infection had an elevated procalcitonin level of >0.5ng/mL. Another study found that only 0.3% of COVID-19 patients had a proven bacterial respiratory infection on admission [5].

Prior to COVID-19, procalcitonin (PCT) was used to differentiate bacterial from viral origins of systemic inflammation with respect to lower respiratory tract infections and sepsis [6–9]. However, procalcitonin elevations have been observed in hospitalized COVID-19 patients leading to difficulties distinguishing viral and bacterial processes [10,13]. One study found that elevated procalcitonin occurred in COVID-19 patients without bacterial pneumonia, and erroneously guided clinicians to prescribe unnecessary antibiotics [11]. A biomarker initially intended as a stewardship tool may actually contribute to excess antibiotic use in the setting of COVID-19 [12]. A recent study confirmed a poor positive predictive value but high negative predictive value of 98.3% with a procalcitonin level of 0.1 ng/mL or less [4]. Our objectives were to evaluate the role of procalcitonin in identifying bacterial co-infections and describe antibiotic use in hospitalized COVID-19 patients.

2. Methods

We conducted a retrospective observational study of COVID-19 patients admitted to an academic medical center in the Bronx, NY in

March and April 2020. Study sites included 3 distinct hospitals within a medical center with an integrated electronic medical record system, unified antimicrobial stewardship and infection prevention programs, and a centralized microbiology laboratory. Throughout the study period, procalcitonin was included in the COVID-19 admissions order set, and guidelines were provided with the result within the electronic health record.

Adult and pediatric patients with a positive SARS-CoV-2 PCR result with a procalcitonin drawn upon admission and a respiratory culture and/or blood culture drawn within 48 hours of the initial procalcitonin were included. We excluded COVID-19 patients who did not have a procalcitonin drawn on admission. Cultures drawn ≥48 hours from the initial procalcitonin or with positive urine cultures only were excluded from the study. During this timeframe, stewardship activities were significantly decreased, as stewards were deployed to assist with COVID-19 therapeutics.

Patient demographics, medical comorbidities, location prior to admission, mechanical ventilation status at time of initial PCT, laboratory results including C-reactive protein (CRP), and antibiotic days of therapy (DOT) were obtained from the electronic medical record. Baseline immunosuppression was defined as chronic diabetes, HIV, chronic hepatitis C, active malignancy, organ transplant, rheumatologic disease, or chronic receipt of immunosuppressive medications. Previously established procalcitonin guidelines at our institution [14] have different PCT thresholds for antibiotic treatment of lower respiratory tract infection (LRTI) (>0.25 ng/mL) and sepsis (>0.5 ng/mL), consistent with established literature. Since moderate-severe COVID-19 in hospitalized patients is a multi-system illness, we selected a more conservative initial procalcitonin threshold of high (>0.5 ng/mL) and low (≤0.5 ng/mL). This cut-off has also been used in other COVID-19 and procalcitonin studies [11,12]. We also conducted sensitivity analyses using cut-offs of >0.25 ng/mL and >1 ng/mL.

An additional analysis was conducted to compare PCT and CRP trends as both are frequently obtained biomarkers in the hospitalized COVID-19 cohort

Initial PCT was chosen as our primary exposure of interest for consistency, as most COVID-19 patients admitted during this timeframe had a procalcitonin ordered from their admission order set.

The primary outcome was confirmed co-infection as determined by the study team based on the following criteria: positive clinical cultures, clinical signs and symptoms consistent with co-infection and EMR documentation by a consulting infectious diseases specialist. Cases requiring adjudication after initial chart review were evaluated by the entire study team. Blood cultures that only grew skin flora, which did not grow in multiple cultures, or on separate dates (i. e., transient growth of gram-positive bacilli, coagulase-negative staphylococci [CONS], micrococci, *Kocuria* spp) were attributed to contamination and categorized as "no confirmed co-infection." Respiratory cultures which exclusively grew yeast, normal oral or respiratory flora, skin flora, or mixed bacterial species were attributed to contamination and categorized as "no confirmed co-infection."[2] Secondary outcomes from throughout the hospitalization included antibiotic use, ICU admission, mortality, and acute kidney injury (AKI), defined as an absolute increase in serum creatinine ≥0.3mg/dL, or an increase in serum creatinine ≥1.5 times baseline.

Albert Einstein College of Medicine institutional review board approved this study with waiver of informed consent.

2.1. Statistical analysis

Bivariate analyses (χ^2, Fisher exact test, t tests, and Wilcoxon rank sums) were conducted, and logistic regression was used to calculate odds ratios (OR). Multivariable logistic regression was conducted to adjust for potential confounders. Analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC). All statistical tests were 2-tailed and *P*-values <0.05 were considered significant.

3. Results

3.1. Patient Demographics and Overall Outcomes

Of the 4762 COVID-19 patients admitted to our medical center between March and April 2020, 3152 (66%) received at least 1 PCT test during their admission, and 1611 (34%) received no PCT tests.

In total, 819 patients were included in this study. Of these, 462 (56%) were men, median age was 63 years (IQR 52−73). Overall, 278 (34%) were Hispanic, 304 (37%) were non-Hispanic Black, and 70 (9%) were White. Eighty percent (659) were admitted from a non-health care facility point of origin. Median BMI was 29.2 kg/m² (IQR 24.6 −33.8), and 246 patients (30%) were defined as immunosuppressed. At the time of PCT test, 200 (24%) required invasive ventilation, and 41 (5%) required non-invasive ventilation. Over the course of hospitalization, 723 (88%) received at least 1 day of antibiotic therapy; the median antibiotic duration was 5 days (IQR: 2-9 days).

Overall, 251 (31%) patients developed acute kidney injury, 269 (33%) were admitted to the ICU, and 300 (37%) patients died during the COVID-19 hospitalization.

3.2. Low versus High Procalcitonin Thresholds

Using institutional PCT cut-offs, 484 (59%) patients had low initial PCT (≤0.5 ng/mL) and 335 (41%) patients had a high initial PCT (>0.5 ng/mL). There were no significant differences in age, sex, race and/or ethnicity, or location before admission between those that had a low versus high PCT, however, patients with underlying immune suppression were more likely to have a high PCT (41% vs 22% *P*-value < 0.001) (Table 1). Forty-two (13%) patients with a high PCT had a confirmed co-infection, compared to 31 (6%) with low PCT (OR = 2.1, *P* = 0.003). Patients with a high PCT were more likely to have AKI (OR = 1.7, *P* = 0.001) and ICU admission (OR = 2.7 *P* < 0.001) during their COVID-19 hospitalization, and had significantly higher mortality (OR = 4.2, *P* < 0.001) (Table 1). These associations between high initial PCT and subsequent AKI (*P* = 0.002), ICU admission (*P* < 0.001), and death (*P* < 0.001), remained statistically significant after adjusting for bacterial infection status.

A comparison of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PCT to detect co-infection in COVID-19 patients is provided in Table 3, using cut-offs of >0.25 ng/mL, >0.5 ng/mL, and >1 ng/mL (Table 3).

3.3. Antibiotic Use

Ninety-six percent (*n* = 323) of patients with an initial high PCT received antibiotics during their hospital stay, compared to 82% (*n* = 397) of patients with a low PCT (*P* < 0.001). Of patients who received antibiotics, ceftriaxone (*n* = 533 74%), vancomycin (*n* = 414 58%), and piperacillin-tazobactam (357 50%) were most frequently administered.

Patients with an initial high PCT had longer median duration of antibiotic therapy (6 vs 4 days, *P*-value < 0.001), and were more likely to receive ≥3 classes of antibiotics (42% vs 15%, *P*-value < 0.01).

3.4. Association between procalcitonin levels, co-infections, and antibiotic use

Overall, 73 (9%) patients had a confirmed co-infection within 48 hours of their initial PCT (Table 1). Patients with confirmed co-infection included 27 (37%) patients with bloodstream infections, 39 (53%) with respiratory infections, and 7 (10%) with both respiratory and bloodstream infections. Patients requiring invasive ventilation were more likely to have a co-infection (32% vs 22%); 34 of 39 (87%) patients with invasive ventilation had a co-infection from a respiratory source (Table 2). The median PCT value for patients with a co-infection

Table 1
Patient characteristics by initial procalcitonin category.

Characteristic	Low procalcitonin (≤0.5 ng/mL) (n = 484)		High procalcitonin (>0.5 ng/mL) (n = 335)		P-value
	n/median	%/IQR	n/median	%/IQR	
Age	63	52-73	63	53-72	0.79
Female	224	46%	133	40%	0.07
BMI	29.4	25.2-34.3	28.80	23.9-33.3	0.71
Immune Suppressed*	108	22%	136	41%	<0.01
Race/Ethnicity					
Hispanic/Latino	169	35%	108	32%	0.35
Non-Hispanic Black	169	35%	135	40%	
Non-Hispanic White	46	10%	22	7%	
Asian	15	3%	14	4%	
Other	33	7%	26	8%	
Unavailable	52	11%	30	9%	
Location Prior to Admission					
Non-healthcare Facility point of Origin	401	83%	257	77%	0.2
Clinic or Physician's Office	12	2%	9	3%	
Transfer from another Hospital or Health Care Facility	12	2%	17	5%	
Transfer From SNF, ICF or ALF	50	10%	44	13%	
Missing	9	2%	8	2%	
Ventilation at time of initial procalcitonin					
Invasive	51	11%	149	44%	
Non-invasive	23	5%	18	5%	<0.001
None	410	85%	168	50%	
Other Labs					
Peak CRP, median (IQR), mg/dL	12.8	4.4-23.3	24.7	11.7-37.5	<0.001
Peak WBC count, median (IQR) k/μL	0.2	0.1-0.5	4.2	1.2-17.5	<0.001
Initial Creatnine	1.0	0.8-1.6	1.3	0.9-3.1	<0.001
Antibiotics					
Received any antibiotics during admission	397	82%	323	96%	<0.001
Received >=3 antibiotic classes during admission	75	15%	140	42%	<0.001
Days of therapy during admission, median	3	1-7	5	2-9	<0.001
Median duration for patients who received antibiotics, days	4	2-7	6.0	3-10	<0.001
Confirmed Co-infection					
Co-infection					
Yes	31	6%	42	13%	0.01
No	453	94%	293	87%	
Co-infection source					
Blood only	11	35%	16	40%	0.27
Respiratory only	19	61%	20	47%	
Both blood and respiratory	1	3%	6	14%	
Outcomes					
AKI	127	26%	124	37%	0.01
Received dexamethasone	21	4%	21	6%	0.26
ICU admission	116	26%	153	46%	<0.001
Death	112	23%	188	56%	<0.001

IQR = inter-quartile range; BMI = body mass index; SNF = skilled nursing facility; ICF = intermediate care facility; ALF = assisted living facility; CRP = C-reactive protein; WBC = white blood count; AKI = acute kidney injury; ICU = intensive care unit.
Baseline immunosuppression was defined as chronic diabetes, HIV, chronic hepatitis C, active malignancy, organ transplant, rheumatologic disease, or chronic receipt of immuno-suppressive medications

was 0.9 ng/mL, compared to 0.3 ng/mL (P-value < 0.001) for those without co-infection (Table 2). Fifty-eight percent (n = 42) of patients with co-infection had an initial PCT >0.5 ng/mL, compared with 39% (n = 293) of patients without a co-infection. Ninety-nine percent (n = 72) of patients with a confirmed co-infection received at least 1 antibiotic day of therapy during their admission and 87% (n = 652) of patients without an initial coinfection received at least

1 antibiotic day of therapy (P-value < 0.001) (Table 2). Patients with a confirmed co-infection were more likely to have AKI (OR = 1.9, P = 0.01), ICU admission (OR = 7.5 P < 0.001), and death (OR = 3.1, P < 0.001) (Table 2).

After adjusting for prior location, age, initial ventilation status, and immune suppression status, PCT >0.5 was not significantly associated with co-infection (OR = 1.1, P = 0.71).

Table 2

Patient characteristics by initial co-infection status.

Characteristic	No co-infection (n = 746)		Confirmed co-infection (n = 73)		P-value
	n/median	%/IQR	n/median	%/IQR	
Age	63	53-73	61	51-70	0.04
Female	327	44%	30	41%	0.35
BMI	29.10	25-33	30.60	25-38	0.40
Immune Suppressed*	212	28%	32	44%	0.01
Race/Ethnicity					
Hispanic/Latino	258	35%	19	26%	0.06
Non-Hispanic Black	269	36%	35	48%	
Non-Hispanic White	65	9%	3	4%	
Asian	27	4%	2	3%	
Other	50	7%	9	12%	
Unavailable	77	10%	5	7%	
Location Prior to Admission					
Non-healthcare Facility point of Origin	605	81%	53	73%	0.08
Clinic or Physician's Office	20	3%	1	1%	
Transfer from another Hospital or Health Care Facility	23	3%	6	8%	
Transfer From SNF, ICF or ALF	82	11%	12	16%	
Missing	16	2%	1	1%	
Ventilation at time of initial procalcitonin					
Invasive	161	22%	39	32%	<0.001
Non-invasive	37	5%	4	3%	
None	548	73%	30	25%	
Other Labs					
Peak WBC count, median (IQR) k/μL	0.5	0.1-4.5	17.5	11.9-25.9	<.0001
Peak CRP, median (IQR), mg/dL	15.6	5.8-28.9	29.9	11.5-41.3	<.0001
Initial Creatinine	1.1	0.8-1.9	1.4	0.9-3.3	0.034
Co-infection					
Blood only			27	37	
Respiratory only			39	53	
Both blood and respiratory			7	10	
Procalcitonin					
Initial procalcitonin, median, (IQR), ng/mL	0.3	0.1-1.3	0.9	0.3-3.8	<.0001
Initial procalcitonin distribution, n (%)					
<0.1 ng/mL	62	8%	2	3%	<.0001
0.1-0.24 ng/mL	286	38%	11	15%	
0.25-0.5 ng/mL	105	14%	18	25%	
>0.5 ng/mL	293	39%	42	58%	
Outcomes					
AKI	219	29%	32	44%	0.006
Received dexamethasone	34	5%	8	11%	0.04
ICU admission	214	29%	55	75%	<.0001
Death	255	34%	45	62%	<.0001

IQR = inter-quartile range; BMI = body mass index; SNF = skilled nursing facility; ICF = intermediate care facility; ALF = assisted living facility; CRP = C-reactive protein; WBC = white blood count, AKI = acute kidney injury; ICU = intensive care unit.

Baseline immunosuppression was defined as chronic diabetes, HIV, chronic hepatitis C, active malignancy, organ transplant, rheumatologic disease, or chronic receipt of immunosuppressive medications

Table 3

Sensitivity and specificity of procalcitonin for co-infections in COVID-19 patients.

	>0.25 ng/mL	>0.5 ng/mL	1 ng/mL
Sensitivity	82%	58%	44%
Specificity	47%	61%	71%
Positive Predictive Value	13%	13%	13%
Negative Predictive Value	96%	94%	93%

However, high PCT was associated with a higher likelihood of initiating antibiotic therapy, even after adjusting for the above criteria. (OR = 3.3, $P < 0.001$).

Thirty-six patients had an initial negative culture, but had subsequent cultures drawn later during the hospital course and at least 1 PCT sent within 48 hours prior to the subsequent culture. Twenty-five of these patients had a confirmed co-infection, and 21 of 25 (84%) of these had a high procalcitonin within 48 hours of positive culture. However, subsequent PCT values were not included in the analysis.

Of the group that did not have PCT sent, 57% received antibiotics during their hospitalization, compared to 88% of patients who had PCT sent (*P*-value < 0.001).

3.5. Procalcitonin and. CRP trends in hospitalized COVID-19 patients

Six hundred and ninety patients had a CRP result during their admission. Median peak CRP value for patients with an initial PCT ≤0.5 ng/mL was 12.8 mg/dL (IQR: 4.4-23.3 mg/dL) compared to 24.7 mg/dL (IQR: 11.7-37.5 mg/dL) for those with an initial high PCT (*P*-value < 0.001) (Table 1). Elevated CRP was also associated with mortality (*P*-value < 0.01) and ICU admission (*P*-value < 0.01), as well as confirmed co-infection (*P*-value < 0.01).

4. Discussion

The primary objective of our study was to assess the role of PCT as a co-infection biomarker in COVID-19 patients. Our results highlight several potential disadvantages of PCT-based antibiotic decision-making in hospitalized COVID-19 patients, especially in absence of antimicrobial stewardship team guidance.

Although patients with a confirmed co-infection had a statistically significant higher median initial PCT (0.9 ng/ml vs 0.3 ng/ml), many patients without co-infection had an elevated PCT (*n* = 293, 39%), which suggests that it is a non-specific tool for concurrent bacterial infection in COVID-19 patients and may instead be elevated due to critical illness and immune activation. Interestingly, 6% of patients in our cohort with low initial PCT ≤0.5 ng/mL had confirmed co-infections, suggesting that PCT was not helpful in this subset of patients either.

Like prior studies [4,15], we observed a low PPV of 13% for co-infected patients, regardless of the PCT threshold utilized. In contrast, an initial PCT of ≤0.5 ng/mL had a high NPV (94%), suggesting that patients with an initially low PCT are highly unlikely to have a bacterial co-infection. Therefore, this threshold can be used for antibiotic discontinuation if started empirically in response to clinical decompensation. Similarly, using a lower cut-off of ≥0.25 ng/ml, one study found that PCT can be used to rule out bacterial co-infection in COVID-19 patients, given its high NPV [15]. Another study found that PCT did not add value to clinical criteria for diagnosis of concurrent bacterial pneumonia regardless of cut-offs used (0.25ng/mL vs 0.5ng/mL). This study also observed high rates of antibiotic use with 86% of patients with an initial high PCT and 66% of patients with an initially low PCT receiving empiric antibiotics for presumed bacterial pneumonia [11].

However, despite high NPV demonstrated in multiple studies, our stewardship team was unable to intervene to discontinue antibiotic therapy on patients with low initial PCT due to competing priorities during the first surge of COVID-19, a phenomenon that was observed by stewardship programs across the country [16].

Low PPV in our study was difficult to interpret because of low overall prevalence of co-infection. However, the study timeframe corresponded with the highest incidence of co-infections at our medical center throughout the pandemic [2].

Of concern, 96% of patients with an initial high PCT and 82% of patients with a low PCT received antibiotics during their hospitalization, with longer DOT and 3 or more antibiotic classes received by the high PCT group. Similarly, 99% of co-infected patients and 87% of non-coinfected patients received antibiotic therapy during admission. Taken together, these findings suggest that PCT did not add value as a stewardship tool in our cohort. After adjusting for potential confounders, including immune suppression, and mechanical ventilation status, patients with high PCT were 3.3 times more likely to be initiated on antibiotic therapy. Therefore, our data suggest that PCT-based antibiotic decision-making might have contributed to increased antibiotic initiations, longer durations of antibiotic therapy, and excess costs related to antibiotic use and laboratory testing.

Likewise, Vaughn et al. observed that half of the patients in their multicenter study received early empiric antibacterial therapy despite a low prevalence of community-onset bacterial coinfections, and that patients with and without bacterial coinfections at presentation both had elevated PCT levels [4]. A recent study suggests that PCT might be a useful biomarker for ventilator-associated pneumonia in COVID-19 patients admitted to the ICU [18]. Given the high NPV, PCT could possibly be utilized as a stewardship tool later on, when COVID-19 patients are at higher risk for health care-associated infections [4,11,17]. Although immunocompromised patients had higher PCT levels, subgroup analysis did not demonstrate a significant association between PCT and co-infections in this group (*P*-value = 0.71).

Independent of co-infection status, PCT elevations are seen with advanced COVID-19. A recent meta-analysis suggests that initial PCT is a marker of disease severity and mortality in COVID-19 patients [19]. Likewise, patients in our study with an initial PCT level >0.5 ng/ml were more likely to have an AKI (OR = 1.7, *P* = 0.001), ICU admission (OR = 2.7 *P* < 0.001), and death (OR = 4.2, *P* < 0.001). Our results are consistent with other studies, suggesting that PCT is a marker of disease severity and mortality in COVID-19 patients independent of co-infection status. Several other biomarkers are utilized for prognostication and management purpose, such as CRP, which may guide diagnostic decisions such as the use of systemic corticosteroids and may also indicate disease severity and risk of death. At our institution, elevated CRP levels of 20 mg/dL or greater, in addition to clinical parameters such as hypoxia, are utilized within a diagnostic algorithm to predict which patients would benefit most from systemic corticosteroid therapy versus those that may be harmed [20,21]. Given the low prevalence of bacterial or fungal co-infections in COVID-19 patients and microbiologic tools with high sensitivity and rapid turn-arounds, such as MALDI-TOF and multiplex PCR panels, co-infection biomarkers may not be necessary [5]. Of note, 57% of patients who did not have PCT sent received antibiotics during their admission, compared to 88% of study participants who had PCT sent, suggesting that PCT-driven management was potentially driving excess antibiotic use.

A limitation of our study is a single-center, multi-site, retrospective study design conducted only over 2 months in 2020, however, our study like others demonstrates low PPV and high NPV of PCT. Additionally, we only included admitted COVID-19 patients who had a PCT and microbiologic cultures sent within 48 hours of each other, which excluded patients without cultures sent who may have been equally ill due to COVID-19. This likely explains the relatively high proportion (9%) of our study participants who had a co-infection, compared to other studies demonstrating a lower prevalence of co-infection between 3% and 8% [1,3,4]. However, the use of strict inclusion and exclusion criteria increases our confidence in the internal validity of results. Another limitation is reporting of 2-year-old data with limited applicability to pandemic surges occurring since 2020. However, in early 2022, hospitals again experienced surges due to the Omicron variant, and excess antibiotic use potentially followed, emphasizing the importance of antibiotic stewardship and appropriate use of biomarkers.

5. Conclusions

Our results suggest that elevated initial PCT levels in hospitalized COVID-19 patients can mislead clinicians toward prescribing antibiotics when no co-infections are present. Antibiotic overuse and increased antibiotic-resistant infections have been well documented in multiple countries throughout the COVID-19 pandemic [4]. Hospitals that routinely obtain admission PCT levels in COVID-19 patients should apply diagnostic stewardship to limit unnecessary testing and antibiotic use.

Declaration of competing interest

All authors report no conflicts of interest relevant to this article.

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