Limited Utility of Procalcitonin in Identifying Community-Associated Bacterial Infections in Patients Presenting with Coronavirus Disease 2019

Michael May,a Michelle Chang,a Donald Dietz,b Sherif Shoucri,b Justin Laracy,b Magdalena E. Sobieszczyk,b Anne-Catrin Uhlemann,b Jason Zucker,b Christine J. Kubinb

aDepartment of Medicine, Columbia University Irving Medical Center, New York, New York, USA
bDepartment of Medicine, Division of Infectious Diseases, Columbia University Irving Medical Center, New York, New York, USA

Jason Zucker and Christine J. Kubin contributed equally to the manuscript.

ABSTRACT The role of procalcitonin in identifying community-associated bacterial infections among patients with coronavirus disease 2019 is not yet established. In 2,443 patients of whom 148 had bacterial coinfections, mean procalcitonin levels were significantly higher with any bacterial infection (13.16 ± 51.19 ng/ml; \( P = 0.0091 \)) and with bacteremia (34.25 ± 85.01 ng/ml; \( P = 0.0125 \)) than without infection (2.00 ± 15.26 ng/ml). Procalcitonin (cutoff, 0.25 or 0.50 ng/ml) did not reliably identify bacterial coinfections but may be useful in excluding bacterial infection.

KEYWORDS antimicrobial stewardship, COVID-19, procalcitonin

Procalcitonin has previously shown promise in distinguishing between bacterial and viral infections, particularly those affecting the lower respiratory tract (1, 2). It has also been studied as a marker for bacterial infections in patients with suspected sepsis (3–5). A precursor to the hormone calcitonin, procalcitonin is stimulated by interleukin 6 (IL-6), tumor necrosis factor, and cytokines associated with bacterial infection and is inhibited by interferon gamma, which is associated with viral infections (6). Clinical studies in patients with pneumonia and bacteremia have demonstrated the potential of a procalcitonin-guided antibiotic management strategy (7, 8). Many hospital guidelines incorporate procalcitonin into treatment algorithms in an effort to promote antibiotic stewardship.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late 2019 and was declared a pandemic by the World Health Organization in March 2020. The utility of procalcitonin in adult patients hospitalized with COVID-19 remains unclear. Whereas procalcitonin values are low in most patients with COVID-19, elevated values have been observed more frequently in severe cases, and some analyses show that elevated procalcitonin is a predictor for clinical deterioration (9–14). However, the value of procalcitonin in distinguishing between bacterial coinfection and systemic inflammation is unknown. In this study, we examine the ability of procalcitonin to identify community-associated bacterial infection (CAI) as defined by positive microbiological results in blood, urine, or respiratory culture within 72 h of presentation in a cohort of patients with COVID-19 at a large medical center in New York City.

We performed a retrospective cohort study of consecutive adults who presented to the emergency department (ED) of New York-Presbyterian/Columbia University Irving Medical Center (NYP/CUIMC) or the Allen Hospital with a positive SARS-CoV-2 result on real-time reverse-transcription PCR (RT-PCR) assay from nasopharyngeal or oropharyngeal swab between 10 March and 30 June 2020. We excluded patients who did not have bacterial infections from our sites of interest but had bacterial infections of peritoneal fluid (\( n = 2 \),...
abscess fluid (3), pericardial fluid (3), wounds (1), lung tissue (1), or other soft tissue (3) within 72 h of presentation. We also excluded patients in whom procalcitonin was not measured within 72 h of presentation. This study was approved by the Columbia University Institutional Review Board with a waiver for informed consent.

We obtained data from the NYP/CUIMC Clinical Data Warehouse, which contains electronic data for inpatient and outpatient visits, including demographics, diagnoses, laboratory tests, and other clinical variables. Diagnoses were extracted from inpatient and outpatient records by searching for diagnosis codes from the International Classification of Diseases, 9th and 10th editions. Data extracted included demographics, labs on first presentation with a positive SARS-CoV-2 RT-PCR, comorbidities, and microbiological results. Of note, our institutional protocol for the care of patients with COVID-19 recommends immediate measurement of procalcitonin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), IL-6, and D-dimer, followed by repeat measurements every 72 h. Thus, the procalcitonin values measured in our study reflect values that were drawn from patients in the ED or shortly after, and we excluded values drawn >72 h after presentation.

We divided patients into those with community-associated bacteremia, bacterial pneumonia, and bacteriuria, as defined by positive microbiological results from the corresponding site, and those without CAI (control). This control group included patients with no positive microbiological results and those who developed bacterial infections >72 h into their admission. We excluded patients with a positive urine culture but an associated urinalysis with <10 white blood cells from our analyses. We evaluated the mean, median, and standard deviation of initial procalcitonin values in these groups. We compared the distribution of initial procalcitonin values in the groups with CAI with those in patients without CAI using a 2-sided t test. P values of <0.05 were considered significant.

We performed analyses on the utility of procalcitonin cutoff values of 0.25 and 0.5 ng/ml to identify the presence of CAI, values studied in the PRORATA and ProHOSP trials (8, 15). These analyses included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). We used Student’s t tests to evaluate significant differences in mean procalcitonin values between groups.

We evaluated 2,443 patients who presented to the ED with COVID-19 during the study period and met inclusion criteria. Of these patients, community-associated bacteriuria, bacteremia, and bacterial pneumonia were identified in 88, 47, and 24 patients, respectively. Only 148 patients accounted for the 159 infections due to the presence of bacterial infections from multiple sources in a small subset of patients. Prevalence of bacterial infection was 6.1%. Subgroup demographics are presented in Table 1.

Of patients with positive urine cultures, the most common genera were Escherichia (59%), Klebsiella (10%), Enterococcus (8%), and Proteus (8%). Of those with bloodstream infections, the most common genera were Streptococcus (21%), Staphylococcus (15%), Escherichia (17%), and Klebsiella (11%). Of patients with staphylococcal bacteremia, 14% (n = 1) had Staphylococcus epidermidis and 86% Staphylococcus aureus infections. Of patients with bacterial pneumonia, the most common genera were Staphylococcus (50%) and Pseudomonas (25%).

Mean procalcitonin levels were significantly higher in patients with any CAI than in those without CAI (13.16 versus 2.00 ng/ml; P = 0.0091). This was driven by patients with bloodstream infections (34.25 ng/ml) more than those with bacteriuria (5.15 ng/ml) or bacterial pneumonia (16.42 ng/ml) (Table 1). A procalcitonin cutoff of 0.25 ng/ml had a sensitivity of 0.568, 0.681, and 0.708; a specificity of 0.527, 0.528, and 0.526; a PPV of 0.043, 0.027, and 0.015; and an NPV of 0.970, 0.988, and 0.995 for detection of community-associated bacteriuria, bacteremia, and bacterial pneumonia, respectively (Tables 2 and 3). Using a procalcitonin level of 0.50 did not significantly change these values (Table 2).

Among other compared inflammatory markers, ferritin and ESR did not differ significantly between groups. Mean IL-6 levels were significantly higher in patients
with bacterial pneumonia (81 pg/ml; \( P = 0.028 \)) and bacteremia (67 pg/ml; \( P = 0.020 \)) than in patients without CAI (40 pg/ml). Mean CRP was also higher in patients with bacterial pneumonia (162 mg/liter; \( P = 0.241 \)) and bacteremia (170 mg/liter; \( P = 0.031 \)) than in those without CAI (133 mg/liter) (Table 1).

This analysis showed that procalcitonin was a poor predictor of CAI among adult patients with COVID-19. Whereas procalcitonin was significantly elevated in patients with CAI compared with uninfected individuals, it demonstrated low sensitivity and specificity for identifying community-associated bacteremia, bacterial pneumonia, and bacteriuria, using a cutoff of 0.25 or 0.5 ng/ml. Although procalcitonin demonstrated an excellent NPV for ruling out CAI, this was likely driven by the low prevalence of CAI. Our findings suggest that elevated procalcitonin in COVID-19 is primarily driven by the inflammation caused by the disease itself rather than by bacterial coinfection. Based on our results, it appears that procalcitonin is not a reliable guide for the decision to initiate antibiotics in patients with COVID-19. Furthermore, the low rate of CAI argues against widespread empirical use of antibiotics in this population.

Strengths of this study include its large number of subjects (2,443). Limitations include our definition of bacterial infection solely as a positive microbiological result without accounting for clinical features. Underestimation of the infection rate is possible if a significant number of patients in our study had bacterial pneumonias, but respiratory cultures were not sent or were negative. Some of our culture results may also represent contaminants rather than true infections. Reassuringly, only one positive blood culture was a coagulase-negative \textit{Staphylococcus} species. Although some small studies have been conducted regarding the utility of procalcitonin in urinary tract infections, data are not definitive in this

### TABLE 1 Demographics of patients included in the study

| Characteristic | All subjects (n = 2,443) | Bacteriuria (n = 88) | Bacteremia (n = 47) | Bacterial pneumonia (n = 24) |
|---------------|-------------------------|---------------------|-------------------|-----------------------------|
| Age (mean [SD] yr) | 65.2 (17.2) | 73.4 (16.7) | 68.1 (15.2) | 58.1 (21.2) |
| Male (n [%]) | 1,395 (57) | 35 (38) | 27 (57) | 10 (42) |
| White (n [%]) | 588 (24) | 33 (38) | 8 (17) | 10 (42) |
| Black (n [%]) | 513 (21) | 11 (12) | 14 (30) | 8 (33) |
| Other/declined (n [%]) | 1,342 (55) | 44 (50) | 25 (53) | 6 (25) |
| Body mass index (median kg/m²) | 27.8 | 26.2 | 24.5 | 24.1 |
| Comorbidity (n [%]) | | | | |
| Chronic obstructive pulmonary disease | 147 (6) | 9 (10) | 9 (19) | 6 (25) |
| Asthma | 251 (10) | 7 (8) | 5 (11) | 3 (13) |
| Hypertension | 1,446 (59) | 55 (63) | 32 (69) | 13 (54) |
| Chronic kidney disease | 280 (11) | 12 (14) | 6 (13) | 3 (13) |
| First ferritin (mean [SD] ng/ml) | 1,214 (2,561) | 1,729 (6,594) | 1,295 (1,572) | 1,084 (1,370) |
| First IL-6 (mean [SD] pg/ml) | 40 (50) | 44 (47) | 67 (68) | 81 (87) |
| First ESR (mean [SD] mm/h) | 72 (33) | 80 (35) | 80 (39) | 64 (39) |
| First CRP (mean [SD] mg/liter) | 133 (94) | 128 (82) | 170 (112) | 162 (117) |

### TABLE 2 Mean procalcitonin levels in community-associated bacterial infections and sensitivity and specificity of initial procalcitonin values of 0.25 and 0.50 ng/ml for identifying community-associated bacterial infections

| Infection type | Procalcitonin level (ng/ml) | Procalcitonin cutoff (ng/ml) of: |
|---------------|-----------------------------|-------------------------------|
|               | Mean [SD] | \( n \) | \( P \) value* | Sensitivity | Specificity | PPV | NPV | Sensitivity | Specificity | PPV | NPV |
| All community-associated infections | 13.16 [5.19] | 148 | 0.0091 | 0.601 | 0.532 | 0.076 | 0.954 | 0.426 | 0.715 | 0.088 | 0.951 |
| Bacteriuria | 5.15 [2.29] | 88 | 0.1428 | 0.568 | 0.527 | 0.043 | 0.970 | 0.363 | 0.710 | 0.045 | 0.967 |
| Bacteremia | 34.25 [8.50] | 47 | 0.0125 | 0.681 | 0.528 | 0.027 | 0.988 | 0.553 | 0.712 | 0.036 | 0.988 |
| Bacterial pneumonia | 16.42 [5.78] | 24 | 0.2345 | 0.708 | 0.526 | 0.015 | 0.995 | 0.500 | 0.709 | 0.017 | 0.993 |
| No infection | 2.00 [1.25] | 2.295 | | | | | | |

*Compared to noninfected patients’ initial procalcitonin using 2-sided t test.
setting (16). Finally, a potential source of bias in this study is the possibility that elevated procalcitonin may have influenced the decision to send cultures.

Our findings indicate that in patients with COVID-19, procalcitonin does not succeed in identifying CAI, although it may have utility in ruling out infection and limiting antibiotic use. Further investigation regarding the role of procalcitonin in patients with COVID-19 is necessary.

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**REFERENCES**

1. Gilbert DN. 2011. Procalcitonin as a biomarker in respiratory tract infection. Clin Infect Dis 52 (Suppl 4):S346–S350. https://doi.org/10.1093/cid/cir050.

2. Self WH, Balk RA, Grijalva CG, Williams DJ, Zhu Y, Anderson EJ, Waterer GW, Courtney DM, Bramley AM, Trabue C, Fakhrian S, Blaschke AJ, Jain S, Edwards KM, Wunderink RG. 2017. Procalcitonin as a marker of etiology in adults hospitalized with community-acquired pneumonia. Clin Infect Dis 65:183–190. https://doi.org/10.1093/cid/cix317.

3. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. 2006. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit Care Med 34:1996–2003. https://doi.org/10.1097/01.CCM.0000226413.54364.36.

4. Becker KL, Snider R, Nylen ES. 2008. Procalcitonin assay in systemic inflammatory response syndrome (SIRS), sepsis, and septic shock: a systematic review. Crit Care Med 36:941–952. https://doi.org/10.1097/01.CCM.0000282184.06280.0d.

5. Tang BM, Eslick GD, Craig JC, McLean AS. 2007. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis 7:210–217. https://doi.org/10.1016/S1473-3099(07)70052-X.

6. Lindscheid P, Seboek D, Nylen ES, Langer I, Schlatter M, Becker KL, Müller B. 2003. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit Care Med 31:1490–1496. https://doi.org/10.1097/01.CCM.0000106672.62086.9F.

7. Meier MA, Branche A, Neeser OL, Wirz Y, Haubitz S, Boudma L, Wolff M, Luyt CE, Chastre J, Tubach F, Christ-Crain M, Corti C, Jensen JS, Deliberato RO, Kristoffersen KB, Damas P, Nobre V, Oliveira CF, Shehabi Y, Stolz D, Tamm M, Mueller B, Schuetz P. 2019. Procalcitonin-guided antibiotic treatment in patients with positive blood cultures: a patient-level meta-analysis of randomized trials. Clin Infect Dis 69:388–396. https://doi.org/10.1093/cid/ciy917.

8. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, Neidert S, Fricker T, Blum C, Schild U, Regez K, Schoenenberger R, Henzen C, Bregener T, Hoesz L, Krause M, Buccheri HC, Zimmerli W, Mueller B, Pro HSG, ProHOSP Study Group. 2009. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA 302:1059–1066. https://doi.org/10.1001/jama.2009.1297.

9. Cecconi M, Piovani D, Brunetta E, Aghemo A, Greco M, Ciccarelli M, Angelini C, Voza A, Omodei P, Vespa E, Pugliese N, Parigi TL, Folci M, Danese S, Bonovas S. 2020. Early predictors of clinical deterioration in a cohort of 239 patients hospitalized for Covid-19 infection in Lombardy, Italy. J Clin Med 9:1548. https://doi.org/10.3390/jcm9051548.

10. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395:507–513. https://doi.org/10.1016/S0140-6736(20)30211-7.

11. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He XJ, Liu S, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen R, Tang CL, Wang T, Cheung P, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS, China Medical Treatment Expert Group for Covid-19. 2020. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 382:1708–1720. https://doi.org/10.1056/NEJMoa2002032.

12. Lippi G, Plebani M. 2020. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chim Acta 505:190–191. https://doi.org/10.1016/j.cca.2020.03.004.

13. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. 2020. Clinical characteristics of 138
hospitalized patients with 2019 novel coronavirus-infected pneumonia in
Wuhan, China. JAMA 323:1061. https://doi.org/10.1001/jama.2020.1585.

14. Zhang JJY, Lee KS, Ang LW, Leo YS, Young BE. 2020. Risk factors of severe
disease and efficacy of treatment in patients infected with COVID-19: a
systematic review, meta-analysis and meta-regression analysis. Clin Infect
Dis 71:2199–2206. https://doi.org/10.1093/cid/ciaa576.

15. Bouadma L, Luýt CE, Tubach F, Cracco C, Alvarez A, Schwebel C,
Schortgen F, Lasocki S, Veber B, Dehoux M, Bernard M, Pasquet B,
Regnier B, Brun-Buisson C, Chastre J, Wolff M, PRORATA Trial Group.
2010. Use of procalcitonin to reduce patients' exposure to antibiot-
ics in intensive care units (PRORATA trial): a multicentre randomised
controlled trial. Lancet 375:463–474. https://doi.org/10.1016/S0140-
6736(09)61879-1.

16. Levine AR, Tran M, Shepherd J, Naut E. 2018. Utility of initial procalcitonin
values to predict urinary tract infection. Am J Emerg Med 36:1993–1997.
https://doi.org/10.1016/j.ajem.2018.03.001.