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Procalcitonin Is Not a Reliable Biomarker of Bacterial Coinfection in People With Coronavirus Disease 2019 Undergoing Microbiological Investigation at the Time of Hospital Admission

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Admission procalcitonin measurements and microbiology results were available for 1040 hospitalized adults with coronavirus disease 2019 (from 48 902 included in the International Severe Acute Respiratory and Emerging Infections Consortium World Health Organization Clinical Characterisation Protocol United Kingdom study). Although procalcitonin was higher in bacterial coinfection, this was neither clinically significant (median [IQR], 0.33 [0.11–1.70] ng/mL vs 0.24 [0.10–0.90] ng/mL) nor diagnostically useful (area under the receiver operating characteristic curve, 0.56 [95% confidence interval, .51–.60]).

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Antimicrobial therapy is not recommended in coronavirus disease 2019 (COVID-19) in the absence of suspected bacterial infection [1]. Meta-analyses of observational data have found that 4.9% of people with COVID-19 present with bacterial coinfection, yet around 75% receive antimicrobials [2, 3].

Procalcitonin production occurs in response to lipopolysaccharide, bacterial infection, and cytokines including interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF- α) [4]. Elevated procalcitonin is used as a biomarker of bacterial infection. In acute respiratory infections, procalcitonin-guided antimicrobial usage can reduce antimicrobial exposure [5]. A substantial increase in this practice has been reported during the COVID-19 pandemic [6]. However, in a cohort of hospitalized people with COVID-19 we have previously reported a stepwise increase in procalcitonin with increasing disease severity [7].

Dysregulated innate immune responses occur in COVID-19 involving a central role for IL-6 [7]. We hypothesized that this could reduce the utility of procalcitonin as a biomarker of bacterial infection. To address this, we aimed to determine whether admission procalcitonin was associated with bacterial coinfection in hospitalized people with COVID-19 undergoing microbiological investigation.

METHODS

Study Design

The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) World Health Organization (WHO) Clinical Characterisation Protocol United Kingdom (CCP-UK) study is an ongoing prospective cohort study recruiting inpatients in 260 hospitals in England, Scotland, and Wales (National Institute for Health Research Clinical Research Network Central Portfolio Management System ID: 14152) performed by the ISARIC Coronavirus Clinical Characterisation Consortium (ISARIC4C). The study protocol is available online (isaric4c.net/protocols). Patients with confirmed or clinician-defined high likelihood of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were eligible for inclusion. Ethical approval was given by the South Central–Oxford C Research Ethics Committee in England (13/SC/0149), the Scotland A Research Ethics Committee (20/SS/0028), and the WHO Ethics Review Committee (RPC571 and RPC572).

Inclusion Criteria for Procalcitonin Analysis

We have reported microbiological findings from 48 902 patients included in the CCP-UK study, hospitalized between

6 February and 8 June 2020, with reverse-transcription polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection and an outcome recorded 28 days after admission [8]. To evaluate the utility of procalcitonin, we retrospectively analyzed a subgroup of this cohort with (1) results of a blood or respiratory culture recorded within 2 days of admission (our previous definition of “coinfection”); (2) a procalcitonin result recorded within 24 hours of admission; and (3) no positive cultures from other sample types in absence of positive blood/respiratory samples. Details of microbiology data processing are included in our previous report [8]. In brief, samples were considered negative if there was no growth or growth suggestive of contamination or colonization (eg, coagulase-negative staphylococci excluding *Streptococcus lugdunensis*, *Corynebacterium* species, or *Cutibacterium* species in blood cultures or *Candida* species in sputum). Samples positive for fungi alone were considered negative for this analysis.

Statistical Analysis

Planned comparisons of procalcitonin values between groups were done using Mann-Whitney tests (Shapiro-Wilk normality test demonstrated a nonnormal distribution). Statistical analyses were performed using GraphPad Prism (version 9.1.2). Relationships between procalcitonin and inflammatory markers (white cell counts, C-reactive protein [CRP], IL-6, TNF- α) were assessed by correlation matrix analysis (using a Spearman test in the *corrplot* R package) or simple linear regression with correlation assessed using a Spearman test.

RESULTS

From the initial cohort of 48 902 patients [8], 8649 had microbiological investigations recorded and 4092 had procalcitonin results recorded. For this analysis, we included 1040 people with both an admission procalcitonin result and microbiological investigations within 2 days of hospital admission (characteristics summarized in [Supplementary Table 1](#)). These patients had a median age of 65 years (interquartile range [IQR], 53–77 years) and 635 (61.1%) were male. Four hundred nine (39.3%) required critical care admission and 301 (29.5%) received invasive mechanical ventilation (IMV). Three hundred forty-six patients died in hospital (33.3%). Compared to the entire initial cohort, patients included in this analysis were younger, more likely to have chest radiograph infiltrates, and more likely to be admitted to critical care and receive IMV; the results of this analysis are therefore more applicable to this subgroup of patients ([Supplementary Table 1](#)).

Blood culture results alone were recorded for 946 (91%) patients, respiratory culture results alone for 58 (5.6%), and both for 36 (3.5%). Overall, 170 (17.3%) blood and 60 (63.8%) of respiratory cultures were positive. Blood and respiratory cultures from 6 patients were both positive but with different pathogens in 5 of 6 cases (in 1 case a β -hemolytic *Streptococcus* was isolated

from both). As previously reported, *Staphylococcus aureus* and gram-negative bacilli were the most prevalent pathogens ([Supplementary Figure 1](#)) [8].

The median admission procalcitonin concentration for patients with any positive culture ($n = 224$) was 0.33 (IQR, 0.11–1.70) ng/mL compared to 0.24 (IQR, 0.10–0.90) ng/mL for negative cultures ($n = 816$; $P = .008$; [Figure 1A](#)). Median procalcitonin for patients with positive blood cultures ($n = 170$) was 0.30 (IQR, 0.10–1.11) ng/mL compared to 0.24 (IQR, 0.10–0.90) ng/mL for negative blood cultures ($n = 812$; $P = .3$). For patients with positive respiratory cultures ($n = 60$), median procalcitonin was 0.90 (IQR, 0.18–4.16) ng/mL compared to 0.71 (IQR, 0.33–2.59) ng/mL for negative respiratory cultures ($n = 34$; $P = .7$). Receiver operator characteristic analysis demonstrated that procalcitonin performed poorly as a diagnostic test (considering any culture result): the area under the curve for classifying absence of coinfection was 0.56 (95% confidence interval [CI], .51–.60; [Figure 1B](#)).

A procalcitonin threshold of 0.25 ng/mL is commonly used in trials of procalcitonin-guided antimicrobial usage (values in health are ≤ 0.04 ng/mL [9]). Observational data demonstrate that using a threshold of ≤ 0.25 ng/mL to advise against empiric antimicrobials in COVID-19 reduces antimicrobial usage [10]. In our cohort, patients with an admission procalcitonin < 0.25 ng/mL were less likely to have a coinfection (91/502 [18.0%] vs 133/538 [24.4%]; $P = .01$), but the sensitivity and specificity of this threshold were low (59.4% [95% CI, 52.8%–65.6%] and 50.4% [46.9%–53.8%], respectively). Similar results were obtained using a threshold of 0.5 ng/mL (sensitivity, 44.2% [37.6%–50.9%]; specificity, 65.4% [62.1%–68.7%]). Since the prevalence of coinfection in this highly selected cohort might not be representative of all hospitalized people with COVID-19, we have deliberately not reported a negative predictive value as it could be misleading.

Correlation matrix analysis identified positive correlations of admission procalcitonin with CRP and total white cell and neutrophil counts ([Figure 1C](#)). This was investigated further using CRP, TNF- α , IL-6, and procalcitonin measurements from plasma samples from hospitalized people with COVID-19 in the ISARIC4C study [7]. Results from the same sample were available for procalcitonin and CRP ($n = 94$), TNF- α ($n = 59$), or IL-6 ($n = 71$). No results of microbiological investigations were recorded for these patients. This identified weak-moderate positive correlations of procalcitonin with CRP ($r = 0.54$, $P < .0001$), TNF- α ($r = 0.36$, $P = .006$), and IL-6 ($r = 0.38$, $P = .001$; [Supplementary Figure 2A–C](#)).

DISCUSSION

Among hospitalized people with COVID-19 undergoing microbiological investigation for suspected bacterial coinfection (within 2 days of admission), admission procalcitonin did not reliably identify people with positive microbiological

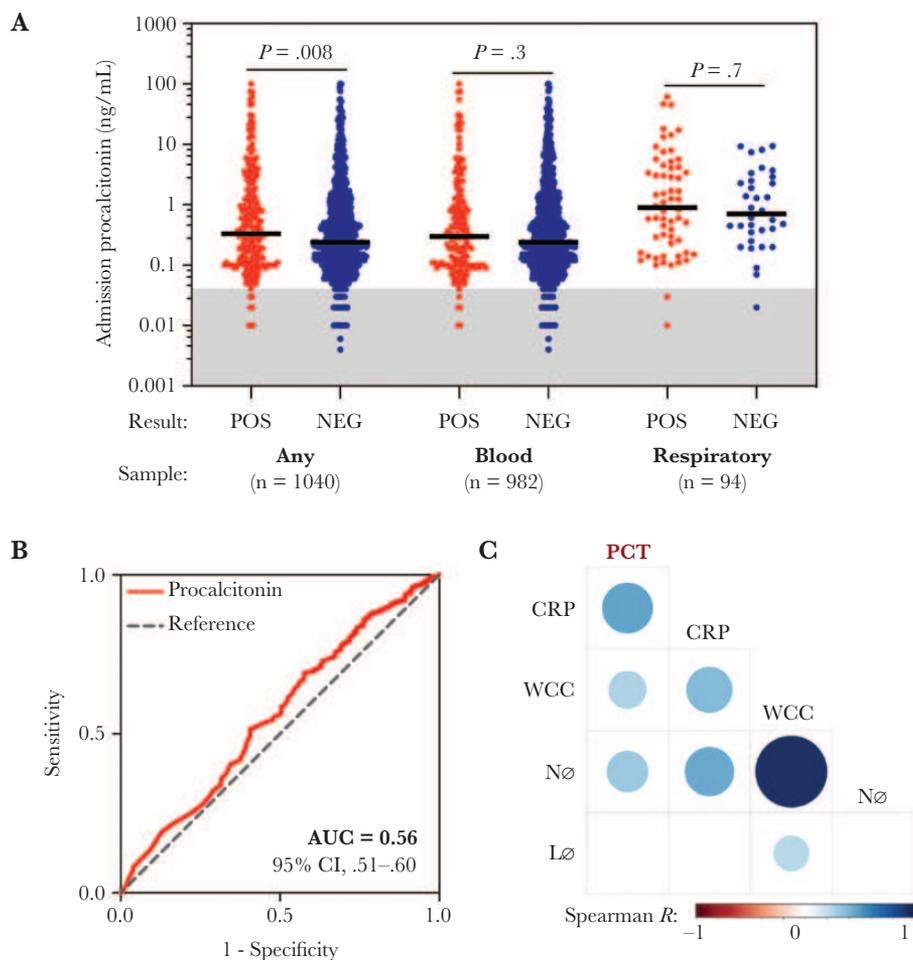


Figure 1. Evaluation of admission procalcitonin as a biomarker of bacterial coinfection in coronavirus disease 2019. *A*, Comparison of admission procalcitonin concentrations between patients with positive and negative microbiology results within the first 2 days of admission. “Any” refers to either blood or respiratory samples, representing the entire cohort. Lines show the median. The gray shading identifies values ≤ 0.04 ng/mL, which is the mean concentration measured in healthy people [9]. Groups were compared with individual Mann-Whitney tests. *P* values shown are uncorrected. *B*, Receiver operating characteristic analysis for admission procalcitonin concentration in predicting absence of coinfection (considering patients with any microbiological sample available). *C*, Correlation matrix analysis of admission procalcitonin, C-reactive protein, total white cell count, neutrophil count, and lymphocyte count. The size and shading of circles represents the Spearman *R* value with a *P* value of < 0.05 . An empty cell indicates no statistically significant correlation between the variables. Abbreviations: AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; LØ, lymphocyte count; NØ, neutrophil count; PCT, procalcitonin; WCC, white cell count.

findings. Low concentrations were observed in some people with coinfection, and high concentrations in some people without. Positive correlations were identified between procalcitonin and inflammatory markers including IL-6.

Procalcitonin is elevated in COVID-19 proportional to disease severity and we propose that IL-6 mediates this independent of bacterial coinfection. In support of this, administration of recombinant IL-6 to humans and stimulation of ex vivo liver slices with IL-6 induces procalcitonin production [11]. In critically ill people with COVID-19, tocilizumab administration is associated with a blunted procalcitonin response to late-onset secondary infections [12]. In a previous study of severe influenza, we found that whole blood transcriptomic signatures characteristic of bacterial infection develop in some patients with severe disease in the second week of illness, associated with

elevated procalcitonin levels without bacterial infection [13]. Severe influenza is also associated with elevated IL-6, at concentrations equivalent to COVID-19 [7, 13]. Observational clinical data from hospitalized people with respiratory virus infections prior to the COVID-19 pandemic (50% with influenza) demonstrates that procalcitonin elevation occurs in pure viral infections, is associated with disease severity, and performs poorly as a diagnostic test for bacterial coinfection [14]. Procalcitonin is also elevated and associated with severity in dengue [15] and Crimean-Congo hemorrhagic fever [16]. Overall, we conclude that procalcitonin may not be a good marker of bacterial infection in viral diseases of sufficient severity to cause hospital admission.

Our retrospective analysis has important limitations. This is a highly selected cohort derived by necessity to address our specific

research question: 1040 of 48 902 (2%) patients in the cohort met inclusion criteria. Selection bias will be present, in particular (1) the degree of clinical suspicion for bacterial coinfection leading to procalcitonin and cultures being performed, (2) ability to obtain microbiological samples, and (3) intersite variability in procalcitonin usage. Rates of recorded microbiological investigation were low and culture positivity was high. There may be a bias for preferential recording of positive microbiology results in the database. Administration of antimicrobials prior to microbiological sampling in community-acquired pneumonia results in false-negative culture results when compared to bacterial PCR [17]. Clinical information regarding bacterial infection diagnosis was not available, meaning coinfection was inferred entirely from microbiology data. Finally, this analysis includes patients from the first pandemic wave in the United Kingdom. Although patterns of secondary infection may differ with subsequent usage of immunomodulators after hospitalization, these changes in practice should not influence the generalizability of our findings to the diagnosis of coinfections at the time of hospital admission. It is important to note that our findings do not relate to use of procalcitonin to diagnose secondary infections (eg, ventilator-associated pneumonia) or serial measurements to observe trends over time in relation to development of secondary infections, where procalcitonin may have greater utility [18].

In conclusion, our study of procalcitonin level at admission to hospital in people with COVID-19 being investigated for suspected bacterial coinfection showed that procalcitonin was not a reliable marker for positive microbiological investigations. Overall, procalcitonin may not be a reliable indicator of bacterial infection in severe viral diseases with raised IL-6 levels. Microbiological investigation remains critical to identify coinfections and inform antimicrobial decision-making.

Notes

Author contributions. C. D. R., A. H., L. T., P. J. M. O., J. K. B., and M. G. S. conceived the study. A. H., C. D. R., L. T., R. P., L. M., S. C. M., A. B. D., R. S. T., S. A., and E. M. H. curated the data. K. A. R., C. D. R., and C. J. F. did the formal analysis. P. J. M. O., J. K. B., and M. G. S. acquired the funding. H. E. H. and W. O. were project administrators. C. D. R., A. H., and M. G. S. supervised the study. K. A. R. and C. D. R. wrote the original draft of the manuscript. A. H., L. T., C. J. F., T. I. d. S., M. K. S., T. M. D., E. M. H., A. B. D., P. J. M. O., J. K. B., and M. G. S. reviewed and edited the manuscript.

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Data sharing. Access to all data and samples collected by ISARIC4C are controlled by an Independent Data and Materials Access Committee composed of representatives of research funders, academia, clinical medicine, public health, and industry. The application process for access to the data is available on the ISARIC4C website (<https://isaric4c.net>).

Patient consent. Consent was not required for collection of depersonalized routine healthcare data for research in England and Wales. A waiver for consent was given by the Public Benefit and Privacy Panel in Scotland. Consent by, or assent for, participants was obtained for additional biological sampling for research purposes

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APPENDIX

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