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ORIGINAL RESEARCH

Infectious Disease

Optimal use of procalcitonin to rule out bacteremia in patients with possible viral infections

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Abstract

Objective: During the winter, many patients present with suspected infection that could be a viral or a bacterial (co)infection. The aim of this study is to investigate whether the optimal use of procalcitonin (PCT) is different in patients with and without proven viral infections for the purpose of excluding bacteremia. We hypothesize that when a viral infection is confirmed, this lowers the probability of bacteremia and, therefore, influences the appropriate cutoff of procalcitonin.

Methods: This study was conducted in the emergency department of an academic medical center in The Netherlands in the winter seasons of 2019 and 2020. Adults (>18 years) with suspected infection, in whom a blood culture and a rapid polymerase chain reaction test for influenza was performed were included.

Results: A total of 546 patients were included of whom 47 (8.6%) had a positive blood culture. PCT had an area under the curve of 0.85, 95% confidence interval (95% CI) 0.80–0.91, for prediction of bacteremia. In patients with a proven viral infection (N = 212) PCT < 0.5 μg/L had a sensitivity of 100% (95% CI 63.1–100) and specificity of 81.2% (95% CI 75.1–86.3) to exclude bacteremia. In patients without a viral infection, the procalcitonin cutoff point of < 0.25 μg/L showed a sensitivity of 87.2% (95% CI 72.6–95.7) and specificity of 64.1 % (95% CI 58.3–69.6).

Conclusion: In patients with a viral infection, our findings suggest that a PCT concentration of <0.50 μg/L makes bacteremia unlikely. However, this finding needs to be confirmed in a larger population of patients with viral infections, especially because the rate of coinfection in our cohort was low.

KEYWORDS
emergency department, infection, procalcitonin, viral infection

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1 | BACKGROUND

Annually more than 20% of adult emergency department visits occur because of severe infections.[1] The most frequent presenting symptoms are fever and respiratory complaints. It is difficult to distinguish between a viral and bacterial cause of these complaints based on clinical symptoms because the complaints in viral and bacterial disease show great overlap.[2,3] During the winter season in the Netherlands, this clinical dilemma is encountered more often as the incidence of viral infections rises. This is usually caused by the annual influenza epidemic; however, in 2020, this epidemic was curtailed by the coronavirus disease 2019 (COVID-19) pandemic. Rapid diagnosis of viral infections has become easier because of the wide availability of a rapid polymerase chain reaction test.[4] However, despite a positive viral test, clinicians often prescribe antibiotics,[5,6] because viral infections predispose patients to bacterial coinfection, especially in the elderly and mortality in those cases is higher.[7–9]

The rate of bacterial coinfection in viral infections is highly variable. In influenza bacterial coinfection rates varying from 2% to 65% have been reported.[7] However, few studies have been conducted in the emergency department (ED), and most of the available data stem from the intensive care unit (ICU). A recent meta-analysis reported a rate of bacterial coinfection in patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) at presentation of 3.5 %.[10] The rate of bacterial coinfections with other viruses such as rhinovirus or respiratory syncytial virus (RSV) has been mostly reported from ICU, which is hard to extrapolate to ED patients.[11]

1.1 | Importance

Estimated rates of unnecessary antibiotic use at the ED are between 30% and 60%, and it has been described as the most preventable cause of antibiotic resistance.[12–14] A recent report by the World Health Organization found that antibiotic resistance could lead to a significant increase in economic costs and 10 million annual deaths globally by 2050 without a sustained effort to contain it.[15]

To reduce antibiotic use and identify bacterial coinfection more accurately, biological markers such as procalcitonin (PCT) have been used but with conflicting results.[16,17].One of the largest studies in the Cochrane meta-analysis of PCT showed high negative predictive value (NPV) of 91.9% for exclusion of a bacterial coinfection in patients admitted to the ICU with influenza, despite a high prevalence of coinfection.[18] A study by Riedel[19] et al showed almost a similar NPV of 96.3% for PCT value 0.1 μg/L in relation to positive blood cultures in patients at the ED, with a sensitivity of 75% and specificity of 76.6%. However, a retrospective study by Goodlet[20] raised concerns on using PCT as a rule-out tool, due to limited sensitivity.

One of the explanations for the different results might be that PCT has been used with several cutoffs ($<0.10\,\mu$g/L, $<0.25\,\mu$g/L, $<0.5\,\mu$g/L). In a review of PCT algorithms, it was advised to take the pretest likelihood of bacterial infection into account to choose the appropriate cutoff.[20–23]

The Bottom Line

Unnecessary antibiotic use in viral infections may be prevented by using procalcitonin levels to rule out a bacterial coinfection. This single-center prospective study of 546 emergency department patients with 212 viral infections had 8 (3.8%) with concomitant positive blood cultures, all of whom had a procalcitonin >0.5 mg/L. This suggests that a procalcitonin level <0.5 mg/L makes bacteremia less likely in the setting of a confirmed viral infection.

1.2 | Goals of this investigation

The aim of this study was to investigate if the PCT cutoff to exclude bacteremia should be different in patients with and without confirmed viral infections, presenting during a viral epidemic or pandemic. We hypothesized that if a viral infection was found, this lowered the probability of bacteremia and therefore influenced the appropriate cutoff of PCT.

2 | METHODS

2.1 | Design setting

This study was observational and the PCT values were not used in clinical practice at the time. The study was conducted prospectively. The study was approved by the local medical ethics committee, a waiver for informed consent was obtained.

The study was planned to run during 2 winter seasons, with the aim to use the influenza seasons. The first inclusion period was from January 2019 to April 2019, and the second inclusion period was from January 2020 until April 2020, coinciding with the start of the COVID-19 pandemic.

2.2 | Setting

The Amsterdam University Medical Center (UMC) is a large teaching hospital with an estimated 30,000 ED presentations annually. Amsterdam UMC is an academic hospital with different training programs including emergency medicine residency training. Most patients seen in our ED were either referred by a general practitioner for acute review or are undergoing outpatient treatment at our facility.

2.3 | Participants

All patients 18 years and older for whom a blood culture and a viral test were ordered in the ED were included. This was a consecutive sample of patients.

2.4 | Exposures

In our hospital, testing for influenza, was based on the case definition of the National Institute for Public Health and Environment, which includes fever and respiratory symptoms.[24] Testing for the novel SARS-CoV-2 was based on the clinical case definition of the National Institute for Public Health and Environment in March 2020. A blood culture was drawn when a bacterial coinfection was suspected by the treating physician. In all included patients, PCT was determined in the blood sample that was drawn for other biochemical tests. No additional sample was needed for this study. Patients were treated according to standard care. Patients were excluded if a blood culture, PCT, or viral test was not available.

2.5 | Measurements

Bacteremia was defined as true positive blood cultures. All blood cultures are processed with the BACTEC system (Becton Dickinson). Culture results were reported in the electronic health system (EPIC). Positive blood culture results were routinely reviewed by a microbiologist. To establish true positivity, the student entering the patients' data in Castor checked if a microbiologist had written a comment on the culture result. In case no microbiologist assessment was available, contamination was assessed according to pre-established criteria (National Nosocomial Infection Surveillance parameters and surveillance criteria for bloodstream infection).[25] In the final data set, contaminated cultures were reclassified as negative cultures. PCT was measured using the Elecsys BRAHMS PCT assay. Viral testing was performed by Cepheid Xpert Flu A/B/RSV XC assay in 2019 and by the Cepheid Xpert SARS-CoV-2/Flu/RSV assay in 2020. If more extensive viral testing was deemed indicated by the treating physician, the result was used in our analysis. All patients with a positive viral test were considered to have a confirmed viral infection.

We identified eligible patients through the microbiology orders. The microbiology laboratory generated a list of patients for the research team in whom both a viral test and a blood culture was ordered in the ED, once a week. Baseline data of patients were then gathered from the electronic health record by trained students, using a script and predefined answer fields. These data were entered in a clinical data management platform, Castor EDC,[26] in compliance with Good Clinical Practice regulations.

2.6 | Outcome

The primary outcome was the diagnostic accuracy of PCT to exclude bacteremia at the predefined cutoffs of < 0.10 μg/L, < 0.25 μg/L, < 0.5 μg/L, overall, and in subgroups based on results of viral testing. The diagnostic accuracy of PCT was defined as the sensitivity, specificity, positive/negative predictive value, likelihood ratio (LR), and the area-under-the-curve (AUC) in excluding bacteremia.

Secondary outcomes were the difference between incidence of bacteremia in patients with and without viral infection and the use of antibiotics.

2.7 | Statistical analysis

All data analyses were performed in SPSS version 26. Normally distributed continuous variables were expressed by their mean and SD. Continuous variables that were not normally distributed were expressed by their median and interquartile range (IQR). Comparison of continuous values, not normally distributed was done with a non-parametric test (Mann Whitney). Analysis of proportions was done with chi-square test (dichotomous variables). Receiver operating characteristic (ROC) curves were drawn to assess the overall diagnostic accuracy of PCT by calculating the AUC with confidence intervals (CI). Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV), and the LR were calculated using MedCalc version 19.4 (MedCalc Software, Ostend, Belgium).

2.8 | Sensitivity analysis

Due to the pandemic, SARS-CoV-2 infection heavily influenced the group of patients with a viral infection, because 109 of the 210 patients with viral infection had COVID-19. Therefore, we performed an additional analysis of the AUROC of PCT in the patients with a viral infection but excluding the patients with COVID-19.

2.9 | Reporting

Reporting was done in concordance with the guideline for Standards for Reporting diagnostic Accuracy (STARD) 2015.[27]

3 | RESULTS

3.1 | Population

During the study period a total of 767 patients presented with suspected infection at the ED. A total of 221 patients were excluded because of missing data; they lacked either blood culture (n=212), PCT (n=30), or both values. Figure 1 displays the diagram of flow of participants. The final study population included 546 patients. Patient demographics are described in Table 1. Forty-seven patients (8.6%) had a true positive blood culture. Fourteen blood cultures were classified as contaminated. Details of the contaminated cultures are described in Table S1. Of the 546 patients, 212 patients (38.8%) had a viral infection. Infection with SARS-CoV-2 was the most frequently diagnosed viral infection (N= 109), followed by influenza A/B (N=62). More details of viral test results can be found in Table S2.

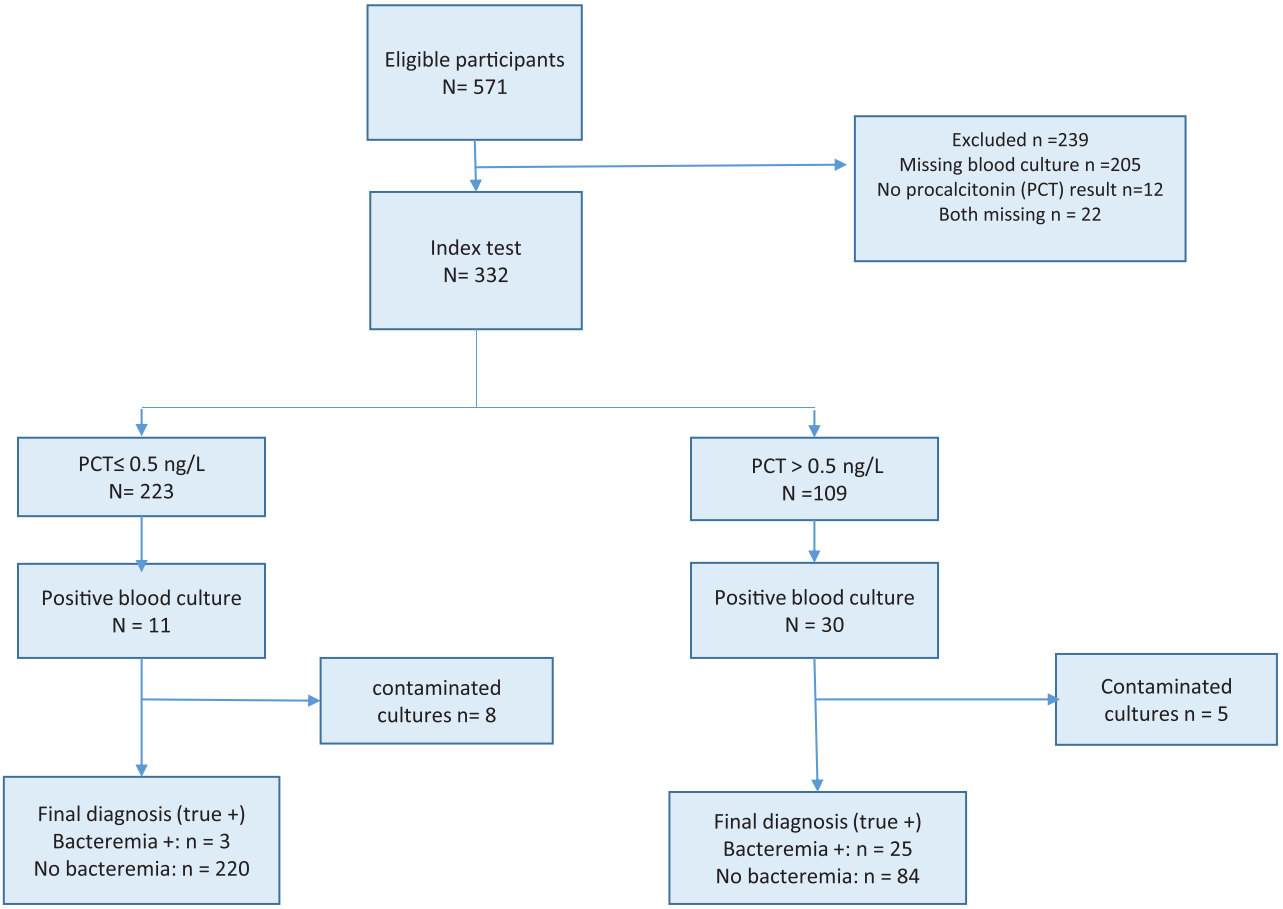

FIGURE 1 Diagram of flow of participants through the study

3.2 | Overall diagnostic value of procalcitonin for bacteremia

The median PCT in the total study population (n=546) was 0.15 μg/L (IQR 0.06–0.57). The area under the curve (AUC) was 0.86 (95% CI 0.81–0.91) and is displayed in Figure 2. The sensitivity, specificity, PPV and NPV, and LRs at the prespecified cutoffs are presented in Table 2.

3.3 | Probability of bacteremia in patients with and without viral infection

Eight of the 212 patients (3.8%) with a confirmed viral infection had bacteremia. In the patients without a viral infection, 39 of the 334 (11.7%) had bacteremia. This was a significant difference, *P* value 0.001 (chi-square test).

3.4 | Diagnostic accuracy of procalcitonin in patients with a proven viral infection

In patients with a viral infection (N=212), median PCT was 0.14 μg/L (IQR 0.07–0.34). The AUC of PCT for prediction of bacteremia was 0.97 (95% CI 0.94–1.00), displayed in Figure 3. All 8 patients with a viral infection and bacteremia had a PCT value of ≥ 0.5 μg/L. The sensitivity, specificity, PPV and NPV, andLRs at the prespecified cutoffs are presented in Table 3. In the group with a viral infection, the sensitivity was 100% (95% CI 63.1–100) and specificity was 81.2% (95% CI 75.1–86.3).

3.5 | Diagnostic accuracy in patients without viral infection

In patients without confirmed viral infection (n = 334), the median PCT was 0.13 (IQR 0.05–0.48). Of the 39 patients in this group with a positive blood culture, 28 had a PCT concentration of ≥ 0.5 μg/L. Of the other 11 patients with positive blood cultures, 2 had a PCT < 0.10 μg/L. Three had a PCT ≥ 0.10 μg/L but <0.25 μg/L, and 6 had a PCT ≥ 0.25 μg/L but <0.5 μg/L. The AUC of PCT for the outcome of bacteremia was 0.83 (95% CI 0.76–0.88). The sensitivity, specificity, PPV and NPV, and LRs are presented in Table 4.

3.6 | Patients with low procalcitonin and positive blood cultures

Eleven patients had a PCT < 0.5 μg/L but a true positive blood culture. None had a proven viral infection. The patient characteristics are summarized in Table S3. None of these patients died within 30 days of this

TABLE 1 Demographics

General characteristics	Study population n = 546
Gender	
Female, N (%)	245 (44.9)
Age, y, mean (SD)	64.0 (17.0)
Admission	
Hospital admission, n (%)	363 (66.5)
ICU admission, n (%)	45 (8.2)
Readmission (30-days), n (%)	47 (8.7)
Comorbidities	
Respiratory disease[a], n (%)	89 (16.4)
Diabetes mellitus, n (%)	94 (17.3)
Vital parameters	
Respiratory rate, mean (SD)	21.7 (7.2)
Oxygen saturation levels, mean(SD)	95.3 (3.9)
Temperature °C, mean (SD)	37.4 (1.3)
MEWS score (median with IQR)	2.0 (2–4)
Laboratory tests (median with IQR)	
CRP (mg/L)	55.0 (17.0–115)
PCT (ng/mL)	0.15 (0.06–0.57)
Positive SARS-CoV-2 PCR (%)	106 (19.5)
Positive blood culture (%)	47 (8.6)
30-days mortality n (%)	63 (11.5)

Abbreviations: CRP, c-reactive protein; IQR, interquartile range; MEWS, modified Early Warning Score; PCR, polymerase chain reaction; PCT, procalcitonin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Emphysema, asthma, and chronic obstructive pulmonary disease.

episode. Five patients had bacteremia and a PCT < 0.25 μg/L. The time between onset of complaints and the first laboratory measurement of PCT (Δ time) was less than 24 hours in all these patients.

3.7 | Use of antibiotics

Of the total of 543,288 patients (53.0%) received antibiotics at the ED, including 37 patients with a positive blood culture. In patients with a confirmed viral infection, 107 of the 210 (50.9%) patients were treated with empirical antibiotics in the emergency department. Of these 107 patients, 74 (69.1%) had a PCT < 0.5 μg/L.

Of the patients without a viral infection (n=333), 180 (54.0%) patients were treated with empirical antibiotics in the ED. Of these patients, 71 (39.4%) had a PCT < 0.25 μg/L.

The most frequent administered antibiotic class were cefalosporines intravenous (n= 154, 51.8%). The median duration of given antibiotics was 6 (IQR 5–7) days.

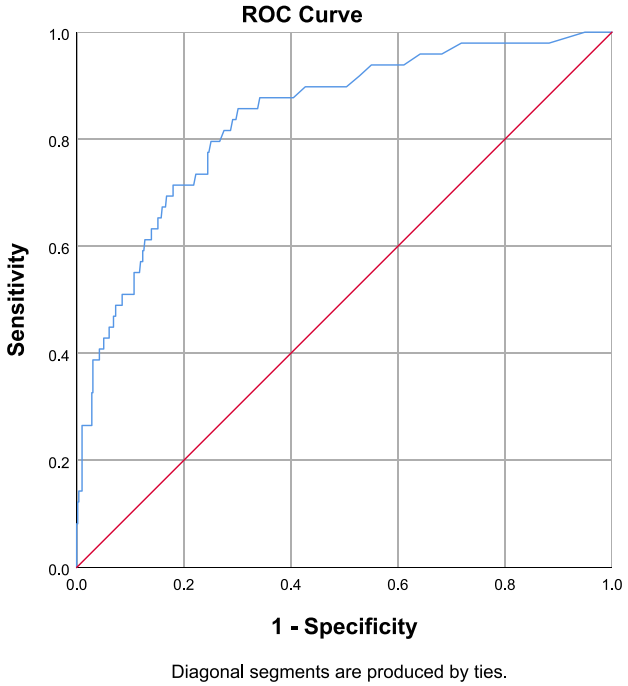

FIGURE 2 ROC curve of procalcitonin for the outcome of bacteremia, total group. Abbreviation: ROC, receiver operating characteristic

3.8 | Sensitivity analysis excluding SARS-CoV-2 patients

In 103 patients with a viral infection, but not SARS-CoV-2 the AUC of PCT for prediction of bacteremia was 0.96 (95% CI 0.90–1.00). The difference was not statistically significant, when compared to the AUC of the total population of patients with a viral infection of 0.96 (95% CI 0.93–0.995).

TABLE 2 Diagnostic accuracy PCT in predicting positive blood culture in total study population

Groups	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR + (95% CI)	LR- (95% CI)
PCT ≥ 0.10	95.7 (85.5–99.5)	38.9 (34.6–43.4)	12.9 (15.9–18.6)	99.0 (96.1–99.7)	1.57 (1.43–1.72)	0.11 (0.03–0.43)
PCT ≥ 0.25	89.4 (76.9–96.5)	65.7 (61.3–69.8)	25.7 (22.8–28.8)	97.90 (95.3–99.0)	2.61 (2.23–3.05)	0.16 (0.07–0.37)
PCT ≥ 0.50	76.6 (62.0–87.7)	77.6 (73.9–81.3)	24.5 (20.5–28.9)	97.2 (95.5–98.3)	3.44 (2.74–4.32)	0.30 (0.18–0.51)

Abbreviations: CI, confidence interval; LR +, positive likelihood ratio, LR-, negative likelihood ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value.
All values are percentages, with the 95% confidence interval between brackets.

TABLE 3 Diagnostic accuracy of PCT in predicting positive blood culture in study population with positive viral test (low-pretest probability)

Groups	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR + (95% CI)	LR- (95% CI)
PCT ≥ 0.10	100 (63.1–100)	34.0 (27.5–41.0)	5.65 (5.14–6.20)	100	1.51 (1.37–1.67)	0.00
PCT ≥ 0.25	100 (63.1–100)	68.0 (61.1–74.4)	11.0 (9.17–13.1)	100	3.12 (2.56–3.82)	0.00
PCT ≥ 0.50	100 (63.1–100)	81.2 (75.1–86.3)	17.4 (13.7–21.9)	100	5.21 (3.93–6.90)	0.00

Abbreviations: CI, confidence interval; LR +, positive likelihood ratio, LR-, negative likelihood ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value.

TABLE 4 Diagnostic accuracy of PCT in predicting positive blood culture in study population with negative viral test (high pretest probability)

Groups	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR + (95% CI)	LR- (95% CI)
PCT ≥ 0.10	94.9 (82.7–99.4)	42.0 (36.4–48.0)	17.8 (16.1–19.6)	98.4 (94.1–99.6)	1.64 (1.45–1.85)	0.12 (0.03–0.47)
PCT ≥ 0.25	87.2 (72.6–95.7)	64.1 (58.3–69.6)	24.3 (21.0–28.3)	97.4 (94.3–98.9)	2.43 (2.00–2.96)	0.20 (0.09–0.45)
PCT ≥ 0.50	71.8 (55.1–85.0)	75.6 (70.3–80.4)	28.0 (22.7–34.0)	95.3 (92.4–97.1)	2.94 (2.22–3.90)	0.37 (0.23–0.62)

Abbreviations: CI, confidence interval; LR +, positive likelihood ratio, LR-, negative likelihood ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value.

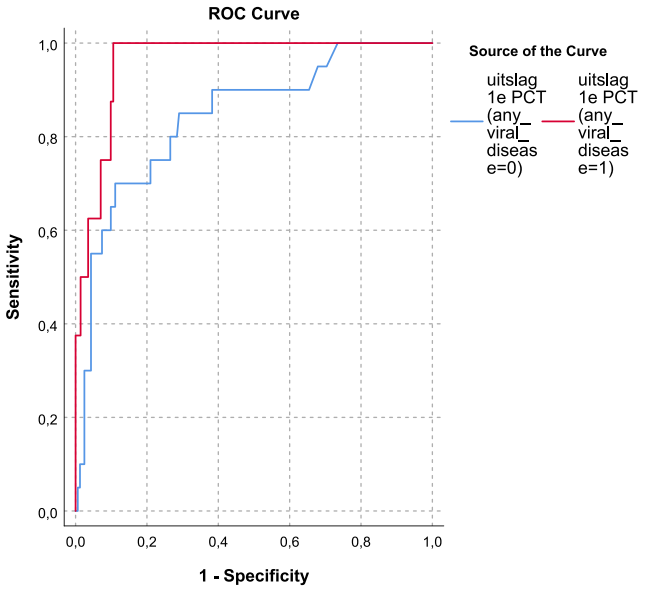

FIGURE 3 ROC curve of procalcitonin for the outcome of bacteremia, split by viral infection. Abbreviations: PCT, procalcitonin; ROC, receiver operating characteristic

3.9 | Limitations

An important limitation is that this study focuses on bacteremia. Blood cultures are the gold standard for detecting bacteria in blood. However, a negative blood culture is no guarantee that there is no bacterial infection. Patients with pneumonia have low rates of bacteremia.[28] In addition, patients previously treated with antibiotics before presentation at the ED might have lower yield of blood culture.[29] Another limitation is that this study has a very low rate of bacterial coinfection. This may limit the generalizability of our findings. However, the rate of coinfection in COVID-19 has been reported as 3.5%, which is comparable to our findings. The low rate of coinfection we found is probably explained by our choice to focus solely on bacteremia. Coinfection in influenza literature has been defined in variable ways, which contributes to the large variation of coinfection rates. In addition, most of the studies on influenza coinfection have been performed in the ICU.[7]

However, it is important that the results of our study are confirmed in a larger sample of patients, with particular attention for the incidence of bacteremia in patients with influenza.

Another limitation is that it was done in a single center in the Netherlands, with a specific case mix. First of all, because of a strong primary care system, almost all patients in the Netherlands are seen first by a general practitioner, who does not refer uncomplicated cases of (viral) infection. Because of this selection, patients presenting to our ED probably represent a subgroup of patients with more severe illness. This is reflected in the high number of admissions in our cohort (68%). Second, the population of our tertiary ED has a higher proportion of patients with malignancies and immunosuppressive treatments. This might influence the probability of bacteremia and limit external validity.

Although all patients underwent influenza A/B/RSV, and in 2020 SARS-CoV-2 testing, we did not limit our analysis to patients with influenza, RSV, and SARS-CoV-2. We pooled all viral infections that were found, because we expected any viral explanation for infectious complaints would make the chance of also having bacteremia smaller. In SARS-CoV-2 infection it has become clear that the incidence of bacterial (co)infection is very low. The sensitivity analysis, excluding the SARS-CoV-2 patients, did not meaningfully change our results.

4 | DISCUSSION

Our study found that PCT performed better in patients with a viral infection, with a higher cutoff than in patients without viral infection. Previous publications have already advocated to vary the cutoff of PCT

based on the likelihood of (severe) bacterial infection. Our insight in the low rate of bacteremia in patients with a confirmed viral infection can help us estimate this likelihood. In our study, PCT was above ≥ 0.5 μg/L in all patients with a viral infection and bacteremia.

Up to 2020, not many studies specifically reported the performance of PCT in the context of proven viral infection. A large observational study [18] on influenza patients in the ICU found that low serum levels of PCT were an accurate predictor for excluding community acquired coinfection during H1N1. The authors reported that PCT is a promising tool, although sensitivity at the cutoff of < 0.50 ng/mL was only 78%. However, because this study was conducted in ICU patients it represented a much sicker population than our target population.

In the context of COVID-19, several studies have reported on PCT values. In most patients PCT was only mildly elevated, and higher levels were usually associated with bacterial coinfections.[30,31] A meta-analysis of PCT in COVID-19 also noted this but described an urgent need for better data.[32] A few small studies have found favorable results on the use of PCT for antibiotic stewardship in COVID-19.[33–35] Despite the limited evidence, our study points in a similar direction as the aforementioned literature.

What this study adds to the current knowledge of PCT is that the results of (rapid) viral testing in the ED can be used to estimate the likelihood of bacteremia. If a viral infection is confirmed and the patient has PCT < 0,5 μg/L, the chances of bacteremia might be very small. If we are informed that the patient has a very low chance of bacteremia, we might be able to make better decisions on antibiotic use. In fact, if we had used PCT as guidance for antimicrobial therapy, antibiotic use could have been decreased from 50.9% to 21.9% in the patients with a viral infection. However, in the group without viral infection, a cutoff of <0.25 μg/L would have resulted in a much smaller reduction of 54% to 42%. In this group we would have missed 5 patients with positive blood cultures, all of whom had symptoms of less than 24 hours duration. This is a known pitfall of PCT because earlier studies have shown that it can take 8–24 hours before PCT reaches high values.[19,20] Therefore, when patients present early after onset of symptoms, PCT should not be regarded as representative. In these cases, the PCT measurements should be repeated to ensure it is representative, in line with previous recommendations.[21]

Our results indicate that PCT is a promising tool to rule out bacteremia in patients with a viral infection. This finding needs to be confirmed in a larger population of patients with viral infections, especially because the rate of coinfection in our cohort was low. In patients without a viral infection, PCT needs to be interpreted with caution, especially in patients with a short duration of symptoms.

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CONFLICTS OF INTEREST

None to declare

AUTHOR CONTRIBUTIONS

Kaoutar Azijli, Tanca C. Minderhoud, and Prabath W.B. Nanayakkara developed the research plan. Kaoutar Azijli, Tanca C. Minderhoud, Carlijn J. de Gans, and Carlijn J. de Gans designed the study. Carlijn J. de Gans, with the help of Kaoutar Azijli, Arthur W.E. Lievel, and Prabath W.B. Nanayakkara collected the data and created the database. The database was checked by Tanca C. Minderhoud. Carlijn J. de Gans, Tanca C. Minderhoud, and Kaoutar Azijli analyzed the data. Carlijn J. de Gans drafted a first version of the paper. Tanca C. Minderhoud and Kaoutar Azijli wrote the definite version of the paper. All authors critically appraised the paper, revised where appropriate and approved the final version of the manuscript. Tanca C. Minderhoud designed the visual abstract.

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REFERENCES

1. Wang HE, Jones AR, Donnelly JP. Revised National estimates of emergency department visits for sepsis in the United States. *Crit Care Med*. 2017;45(9):1443-1449.
2. Angeles Marcos M, Camps M, Pumarola T, et al. The role of viruses in the aetiology of community-acquired pneumonia in adults. *Antivir Ther*. 2006;11(3):351-359.
3. Huijskens EGW, Koopmans M, Palmen FMH, van Erkel AJM, Mulder PGH, Rossen JWA. The value of signs and symptoms in differentiating between bacterial, viral and mixed aetiology in patients with community-acquired pneumonia. *J Med Microbiol*. 2014;63(3):441-452.
4. Vos LM, Bruning AHL, Reitsma JB, et al. Rapid molecular tests for influenza, respiratory syncytial virus, and other respiratory viruses: a systematic review of diagnostic accuracy and clinical impact studies. *Clin Infect Dis*. 2019;69(7):1243-1253.
5. Havers FP, Hicks LA, Chung JR, et al. Outpatient antibiotic prescribing for acute respiratory infections during influenza seasons. *JAMA Network Open*. 2018;1(2):e180243-e180243.
6. Langford BJ, So M, Raybardhan S, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. *Clin Microbiol Infect*. 2021;27(4):520-531.
7. Klein EY, Monteforte B, Gupta A, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. *Influenza Other Respir Viruses*. 2016;10(5):394-403.
8. Metersky ML, Masterton RG, Lode H, File TM, Jr., Babinchak T. Epidemiology, microbiology, and treatment considerations for bacterial pneumonia complicating influenza. *Int J Infect Diseas*. 2012;16(5):e321-331.
9. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin Microbiol Rev*. 2006;19(3):571-582.
10. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clin Microbiol Infect*. 2020;26(12):1622-1629.
11. Cawcutt K, Kalil AC. Pneumonia with bacterial and viral coinfection. *Curr Opin Crit Care*. 2017;23(5):385-390.
12. Minderhoud TC, Spruyt C, Huisman S, Oskam E, Schuit SCE, Levin MD. Microbiological outcomes and antibiotic overuse in emergency department patients with suspected sepsis. *Neth J Med*. 2017;75(5):196-203.
13. May L, Cosgrove S, L'Archeveque M, et al. A call to action for antimicrobial stewardship in the emergency department: approaches and strategies. *Ann Emerg Med*. 2013;62(1):69-77.e62.

14. Denny KJ, Gartside JG, Alcorn K, Cross JW, Maloney S, Keijzers G. Appropriateness of antibiotic prescribing in the emergency department. *J Antimicrob Chemother*. 2019;74(2):515-520.
15. WHO. NO TIME TO WAIT: ECURING THE FUTURE FROM DRUG-RESISTANT INFECTIONS. 2019. https://www.who.int/publications/i/item/no-time-to-wait-securing-the-future-from-drug-resistant-infections
16. Kamat IS, Ramachandran V, Eswaran H, Guffey D, Musher DM. Procalcitonin to distinguish viral from bacterial pneumonia: a systematic review and meta-analysis. *Clinical Infect Dis* . 2020;70(3):538-542.
17. Schuetz P, Wirz Y, Sager R, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev*. 2017(10).
18. Rodríguez AH, Avilés-Jurado FX, Díaz E, et al. Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: a CHAID decision-tree analysis. *J Infect*. 2016;72(2):143-151.
19. Riedel S, Melendez JH, An AT, Rosenbaum JE, Zenilman JM. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. *Am J Clin Pathol*. 2011;135(2):182-189.
20. Goodlet KJ, Cameron EA, Nailor MD. Low sensitivity of procalcitonin for bacteremia at an academic medical center: a cautionary tale for antimicrobial stewardship. *Open Forum Infect Dis*. 2020;7(4).
21. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. *BMC Med*. 2011;9:107.
22. Schuetz P, Falsey AR. Procalcitonin in patients with fever: one approach does not fit all. *Clinical Microbiol Infect*. 2018;24(12):1229-1230.
23. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. *Arch Intern Med*. 2011;171(15):1322-1331.
24. dr. A. Meijer RCI. Influenza Richtlijn https://lcirivmnl/richtlijnen/influenza. 2012.
25. Hall KK, Lyman JA. Updated review of blood culture contamination. *Clin Microbiol Rev*. 2006;19(4):788-802.
26. Castor EDC. Castor electronic data capture. https://castoredc.com. Published 2019. Accessed August 28, 2019.
27. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ (Clin Res ed)*. 2015;351:h5527.
28. Kennedy M, Bates DW, Wright SB, Ruiz R, Wolfe RE, Shapiro NI. Do emergency department blood cultures change practice in patients with pneumonia? *Ann Emerg Med*. 2005;46(5):393-400.
29. Nannan Panday RS, Wang S, van de Ven PM, Hekker TAM, Alam N, Nanayakkara PWB. Evaluation of blood culture epidemiology and efficiency in a large European teaching hospital. *PLoS One*. 2019;14(3):e0214052-e0214052.
30. van Berkel M, Kox M, Frenzel T, Pickkers P, Schouten J. Biomarkers for antimicrobial stewardship: a reappraisal in COVID-19 times? *Crit Care*. 2020;24(1):600.
31. Williams P, McWilliams C, Soomro K, et al. The dynamics of procalcitonin in COVID-19 patients admitted to Intensive care unit - a multi-centre cohort study in the South West of England, UK. *J Infect*. 2021;82(6):e24-e26.
32. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chim Acta*. 2020;505:190-191.
33. Heesom L, Rehnberg L, Nasim-Mohi M, et al. Procalcitonin as an antibiotic stewardship tool in COVID-19 patients in the intensive care unit. *J Global Antimicrobial Resist*. 2020;22:782-784.
34. Williams EJ, Mair L, de Silva TI, et al. Evaluation of procalcitonin as a contribution to antimicrobial stewardship in SARS-CoV-2 infection: a retrospective cohort study. *J Hosp Infect*. 2021;110:103-107.
35. Peters C, Williams K, Un EA, et al. Use of procalcitonin for antibiotic stewardship in patients with COVID-19: a quality improvement project in a district general hospital. *Clin Med*. 2021;21(1):e71-e76.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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