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ABSTRACT

Background Guidelines recommend maximal efforts to obtain blood and sputum cultures in patients with COVID-19, as bacterial coinfection is associated with worse outcomes. The aim of this study was to evaluate the yield of bacteriological tests, including blood and sputum cultures, and the association of multiple biomarkers and the Pneumonia Severity Index (PSI) with clinical and microbiological outcomes in patients with COVID-19 presenting to the emergency department (ED).

Methods This is a substudy of a large observational cohort study (PredictED study). The PredictED included adult patients from whom a blood culture was drawn at the ED of Haga Teaching Hospital, The Netherlands. For this substudy, all patients who tested positive for SARS-CoV-2 by PCR in March and April 2020 were included. The primary outcome was the incidence of bacterial coinfection. We used logistic regression analysis for associations of procalcitonin, C reactive protein (CRP), ferritin, lymphocyte count and PSI score with a severe disease course, defined as intensive care unit admission and/or 30-day mortality. The area under the receiver operating characteristics curve (AUC) quantified the discriminatory performance.

Results We included 142 SARS-CoV-2 positive patients. On presentation, the median duration of symptoms was 8 days. 41 (29%) patients had a severe disease course and 24 (17%) died within 30 days. The incidence of bacterial coinfection was 2/142 (1.4%). None of the blood cultures showed pathogen growth while 6.3% was contaminated. The AUCs for predicting severe disease were 0.76 (95% CI 0.68 to 0.84), 0.70 (0.61 to 0.79), 0.62 (0.51 to 0.74), 0.62 (0.51 to 0.72) and 0.72 (0.63 to 0.81) for procalcitonin, CRP, ferritin, lymphocyte count and PSI score, respectively.

Conclusion Blood cultures appear to have limited value while procalcitonin and the PSI appear to be promising tools in helping physicians identify patients at risk for severe disease course in COVID-19 at presentation to the ED.

Key messages

What is already known on this subject

- Reported rates of bacterial coinfection in patients with COVID-19 presenting at the emergency department (ED) are low (0%–8%). Nevertheless, guidelines advise to maximise efforts to collect blood cultures and other microbiological tests, in order to allow restrictive use of antibiotics.
- Early identification of patients with COVID-19 at risk for developing a severe disease course (intensive care unit admission and/or mortality) is important for clinical decision making. Several clinical and biochemical parameters are associated with a severe disease course. However, which parameters are of most value to identify patients at risk for severe disease course when presenting to the ED is unknown.

What this study adds

- In this retrospective study of patients receiving blood cultures at a hospital in The Netherlands, we found that 6.3% of patients with SARS-CoV-2 had positive blood cultures and all were considered contaminated. Overall bacterial coinfection using other diagnostics was 1.4%. This suggests that in patients known to have SARS-CoV-2, blood cultures are unlikely to be of use.
- Procalcitonin and the Pneumonia Severity Index seem most promising to recognise patients at risk for severe outcome of COVID-19 when presenting to the ED.

INTRODUCTION

Since the emergence of COVID-19, knowledge about the disease has quickly advanced. In times where large numbers of patients ask the most from healthcare facilities, it is of great relevance to identify those at high risk of developing a severe disease course. Currently, known risk factors for severe disease, defined as intensive care unit (ICU) admission and/or mortality, include older age and comorbidities such as diabetes, cardiovascular and pulmonary disease.[1 2]

Furthermore, several biomarkers are associated with severe disease course in patients with COVID-19, including C reactive protein (CRP), ferritin, lymphocyte count and procalcitonin (PCT).[3 4] It is well-known that bacterial pulmonary coinfections are a major concern in respiratory viral infections. Zhou *et al* showed that in a cohort of non-survivors of COVID-19, 50% had a secondary infection.[2] Current data on patients with COVID-19 show

that the incidence of bacterial coinfection on admission is relatively low, ranging from 0% to 8%.[5 6] Differentiating between viral or bacterial pulmonary infection can be challenging. In this respect, PCT is a more accurate predictor than CRP in patients with community-acquired pneumonia (CAP) and influenza.[7 8] Therefore, the American Thoracic Society & Infectious Diseases Society of America endorses withholding of antibiotics in patients with non-severe COVID-19 with low PCT levels.[9] The Dutch Working Party on Antibiotic Policy (SWAB) advises a risk-based antibiotic policy based on the Pneumonia Severity Index (PSI) for patients with CAP.[10 11] For patients with COVID-19, restrictive antibiotic use is encouraged except for those in the highest risk group and maximal efforts are recommended to obtain blood and sputum cultures.[12] It recognises that using PCT to guide antibiotic treatment might be a valid strategy, but evidence is lacking.[11 12]

We were able to investigate a subset of patients with COVID-19 from an observational study, evaluating the value of PCT in patients visiting the emergency department (ED) from whom a blood culture was drawn. This gave us the opportunity to explore the previous reported association of PCT with severe course of COVID-19, and to investigate whether this might be explained by the presence of bacterial coinfection. We expected a relatively high rate of bacterial coinfection in this cohort since the performance of a blood culture is an indicator of suspected bacteraemia or sepsis. Besides exploring the role of bacterial coinfection, it is of interest to know which biomarkers are most useful to help physicians recognise patients with COVID-19 at high risk for severe disease when presenting to the ED.

We hypothesise that PCT is superior to more commonly used biomarkers such as CRP, ferritin and lymphocyte count in identifying patients with COVID-19 presenting to the ED with a bacterial coinfection and those who are at risk for a severe disease course. The aim of this study is to explore the incidence of bacterial coinfection and the association of the PSI and multiple biomarkers with clinical and microbiological outcomes in patients with COVID-19 presenting to the ED.

METHODS

Study design and participants

This is a substudy of the PredictED study. The PredictED is a single-centre prospective observational study conducted at the ED of the Haga Teaching Hospital, a large hospital in The Hague, The Netherlands. Annually, around 50 000 patients present to this ED of which the majority are referred by a general practitioner. The PredictED study evaluates PCT as a marker for bacteraemia in patients presenting to the ED. All consecutive patients at the ED aged 18 years or older that had at least one blood culture taken at the treating physician's discretion were included in the PredictED. There were no exclusion criteria. Data collection of the PredictED was set from 1 April 2019 until 30 April 2020, which included the regional peak period of the first wave of the COVID-19 pandemic in the Netherlands during March and April 2020. Within this cohort, all patients with COVID-19 confirmed by a positive PCR test for SARS-CoV-2 were included in the present study. The PredictED study has been registered at trialregister.nl (NL7852; 7 July 2019).

Test methods

A SARS-CoV-2 infection was confirmed using an in-house real-time PCR using a combination of the QIAsymphony and ABI7500 on a nasopharyngeal/throat swab.[13] Blood cultures were incubated using the BacTEC/Alert automated blood culture system. Determination was done with gram stain and with the Bruker Maldi-tof-MS biotyper. Due to the large amount of test requests in this period, standard incubation time was reduced from five to three days. Since PCT is not routinely measured at our ED, PCT was measured using leftover blood that was drawn for chemistry testing during the ED visit. PCT was measured with an automated rapid sensitive assay (Elecsys Brahsm PCT on Roche Cobas E601, Basel, Switzerland, measuring range 0.02–100 ng/mL). The PCT result was not available to the attending physician. Other microbiological tests were performed at discretion of the treating physician. The reference tests were defined as the biomarkers that were measured in a routine test set for suspected patients with COVID-19 attending the ED, namely CRP, ferritin and lymphocyte count.

Definitions

Bacterial coinfection was defined as a positive PCR for *Mycoplasma pneumoniae* or *Chlamydophila* spp, a positive pneumococcal or legionella urinary antigen test or bacterial growth in a blood or sputum culture recognised as a pathogen and not deemed a contaminant as reviewed by three members of our research team (AK, LS and SM). For blood cultures, Coagulase-negative staphylococci, *Bacillus* spp, *Corynebacterium* spp, *Cutibacterium* spp, Viridans group streptococci and *Lactobacillus* spp were considered contaminants unless associated with an intravascular catheter or device, suspected endocarditis or the presence of multiple positive blood cultures with the same bacterium. Microbiological tests performed more than 48 hours after ED presentation were excluded.

Demographics, clinical, biochemical and microbiological results were collected from electronic patient records. The Charlson Comorbidity Index was included as a measure for burden of comorbidities.[14] The PSI score and quick sequential organ failure assessment score were used for disease severity at presentation.[10 15]

Outcomes

The primary outcome was the incidence of bacterial coinfection at ED presentation and its association with PCT. The secondary outcome was severe disease course, defined as admission to the ICU and/or mortality within 30 days. Biomarkers were compared with the PSI score since this is routinely used at our ED to assess the risk of mortality in patients suffering from pneumonia.

Patient and public involvement

No patients were involved in the production of this research.

Statistical methods

Continuous variables are presented as mean±SD or median and IQR. Categorical data are summarised as counts and percentages. Baseline characteristics were compared between groups of severity using χ^2 or Fisher's exact test for categorical variables, and the unpaired t-test or Mann-Whitney U test for continuous variables. Univariate and multivariable logistic regression was used to determine the association between all biomarkers and severe outcome, including age as potential confounder. PCT was also corrected for severe kidney disease, since PCT levels are significantly higher in patients with an advanced stage of chronic kidney disease.[16] Severe kidney disease was defined as patients on dialysis, creatinine >270 µmol/L, uraemia or a history of kidney transplant. Variables were logarithmically transformed in regression analyses. The log2 was used; in this way ORs refer to a doubling in the value of the variable.[17] ORs

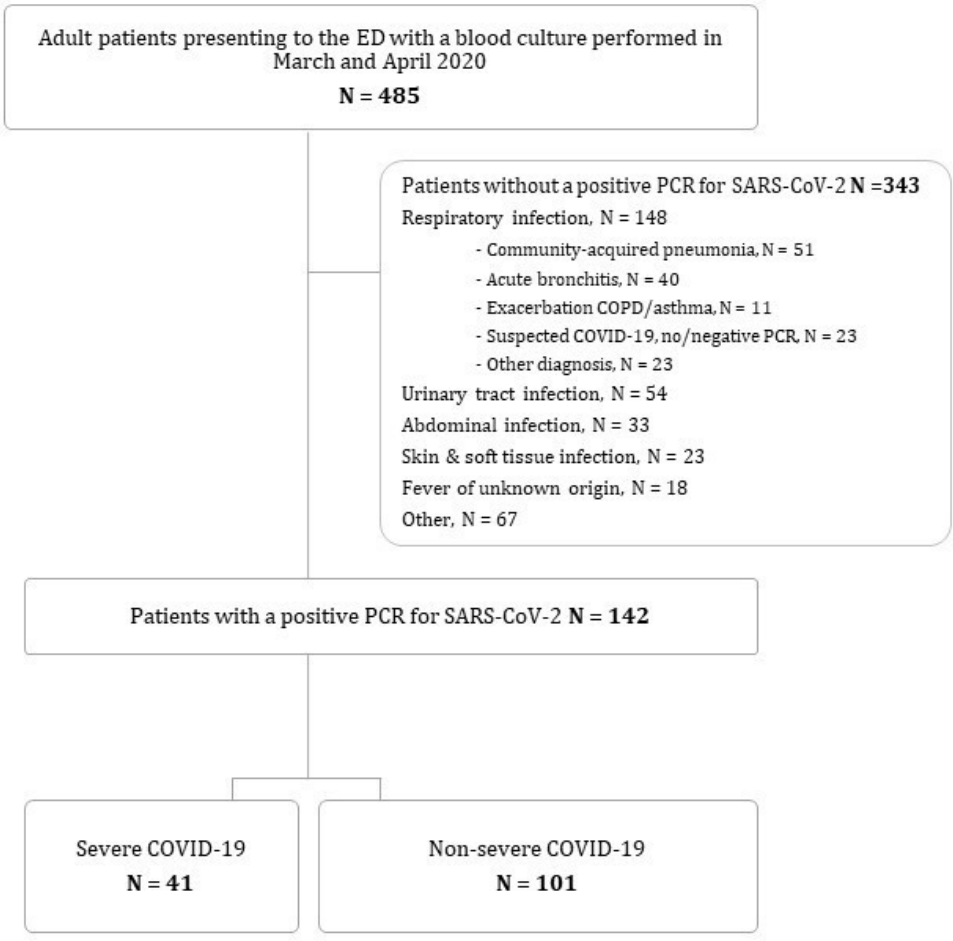

Figure 1 Flowchart of patient inclusion. COPD, chronic obstructive pulmonary disease; ED, emergency department.

were also calculated for pre-defined internationally used cut-off values for PCT (<0.10 ng/mL, 0.10–0.25 ng/mL, 0.25–0.50 ng/mL and >0.50 ng/mL) and pre-defined PSI-categories (PSI 1–5). For this analysis, the non-transformed data was used. The area under the receiver operating characteristics (ROC) curve (AUC) was used to quantify discriminative ability for all biomarkers, PSI score, and for a combination of the biomarker with the highest predictive value and the PSI score. Patients with missing values were excluded per analysis. The number of missing values is reported below each table. Statistical significance was assumed for a p value ≤0.05. All analyses were performed using IBM SPSS statistics V.24.0 (IBM Corp).

RESULTS

In total, 485 ED patients had a blood culture taken in March and April 2020, of whom 142 patients tested positive for SARS-CoV-2 (figure 1). The mean age of the 142 patients was 61 years (SD ±17.1), ranging from 25 to 99 years, of which 66% (93/142) were men. More than half of the patients suffered from any comorbidity, 25% had diabetes, 24% had a history of cardiovascular disease and 20% had a history of pulmonary disease (table 1).

Microbiological findings

In this cohort, 1.4% (2/142) of the patients had a bacterial coinfection at presentation (table 2); antibiotics were prescribed in 32% (46/142); 28% already received antibiotics prior to presentation to the ED (table 1). In the first 48 hours after presentation, 175 blood cultures were taken, resulting in 11 positive cultures from 10 individuals that were all deemed contaminants (online supplemental appendix A). Because there were only two patients with bacterial coinfection, the association between biomarkers and microbiological outcome could not be further investigated.

The first patient had a positive pneumococcal urinary antigen test and a lobar infiltrate on chest X-ray. He was on long-term treatment with prednisone and azathioprine for microscopic polyangiitis. The second patient had a medical history of chronic obstructive pulmonary disease with known colonisation with *Pseudomonas aeruginosa*. In this case, a sputum culture was again positive for *P. aeruginosa*. Neither one had a severe disease course; both recovered after 6 days of admission. A more extensive summary of the clinical presentation of these patients is given in online supplemental appendix B.

Severe disease course

Of 142 patients, 41 patients met the definition for severe disease course; 24 (17%) patients died within 30 days. All patients in the severe disease course group were admitted to the hospital; in the non-severe group, 79 out of 101 (78%) were admitted (table 1). In the severe disease course group, the median Charlson Comorbidity Index was significantly higher compared with the non-severe group (3 vs 2, p<0.01).

The median time since onset of symptoms until presentation at our ED was 8 days (IQR 5). At presentation, the patients with a severe disease course had a higher respiratory rate (30 vs 25, p<0.001) and lower peripheral oxygen saturation (91% vs 95%,

Table 1 Baseline characteristics

	Non-severe, n=101	Severe, n=41	Total, n=142	P value*
Demographics				
Age, mean (SD)	58 (17.1)	69 (14.9)	61 (17.1)	**<0.001**
Males, no (%)	65 (64.4)	28 (68.3)	93 (65.5)	0.65
Nursing home resident, no (%)	9 (8.9)	2 (4.9)	11 (7.7)	0.51
Comorbidities, no (%)				
Any type of comorbidity	66 (65.3)	26 (63.4)	92 (64.8)	0.83
Diabetes mellitus	22 (21.8)	13 (31.7)	35 (24.6)	0.21
Cardiovascular disease†	23 (22.8)	11 (26.8)	34 (23.9)	0.61
Pulmonary disease‡	23 (22.8)	6 (14.6)	29 (20.4)	0.28
Malignancy	11 (10.9)	6 (14.6)	17 (12)	0.57
Neurological disease§	10 (9.9)	6 (14.6)	16 (11.3)	0.40
Renal disease¶	8 (7.9)	4 (9.8)	12 (8.5)	0.74
Charlson Comorbidity Index, median (IQR)	2 (0–3.5)	3 (1.5–4.5)	2 (0–4)	**<0.01**
Symptoms and vital signs at presentation				
Time since onset of symptoms, days, median (IQR)	9 (7–12)	7 (4–11)	8 (6–11)	**0.03**
Temperature, °C, mean (SD)	38.6 (0.9)	38.4 (1)	38.5 (0.9)	0.23
Respiratory rate, breaths/min, mean (SD)	24.9 (6.3)	29.5 (7.6)	26.2 (7)	**<0.001**
Saturation, %, median (IQR)	95 (93–96)	91 (88–95)	94 (91–96)	**<0.001**
Heart rate, beats/min, mean (SD)	98 (17)	99 (20)	98 (18)	0.62
Systolic blood pressure, mm Hg, mean (SD)	129.9 (21.7)	132.2 (31.9)	130.6 (25)	0.62
Diastolic blood pressure, mm Hg, mean (SD)	75.7 (12.7)	75.2 (15.7)	75.6 (13.6)	0.88
Glasgow Coma Score, median (IQR)	15 (15–15)	15 (15–15)	15 (15–15)	0.66
q-SOFA score, mean (SD)	0.7 (0.6)	1 (0.5)	0.8 (0.6)	**<0.01**
PSI score, mean (SD)**	74.2 (31.9)	99.7 (37.5)	82 (35)	**<0.001**
PSI 1, no (%)	22 (21.8)	3 (7.3)	25 (17.6)	
PSI 2, no (%)	30 (29.7)	4 (9.8)	34 (23.9)	
PSI 3, no (%)	20 (19.8)	10 (24.4)	30 (21.1)	
PSI 4, no (%)	24 (23.8)	18 (43.9)	42 (29.6)	
PSI 5, no (%)	5 (5)	6 (14.6)	11 (7.7)	
Use of antibiotics in last 7 days, no (%)	30 (30)	9 (22)	39 (27.7)	0.33
Use of immunosuppressants, no (%)	5 (5)	3 (7.3)	8 (5.6)	0.69
Laboratory findings at admission, median (IQR)				
Creatinine, µmol/L	83 (66–101)	101 (83–137)	87 (69–108)	**<0.001**
LDH, U/L	284 (224–422)	416 (264–517)	317 (234–441)	**<0.01**
Ferritin, µg/L	534 (263–819)	824 (369–1255)	564 (273–987)	**0.03**
Thrombocytes, 10^9/L, mean (SD)	202 (65)	201 (78)	202 (69)	0.94
White blood cell count, 10^9/L	6.3 (5–8.1)	6.8 (5–9.6)	6.6 (5–8.3)	0.22
Lymphocyte count, 10^9/L	1.02 (0.7–1.3)	0.81 (0.6–1.2)	0.96 (0.7–1.3)	**0.03**
CRP, mg/L	74 (35–122)	127 (82–203)	86 (44–142)	**<0.001**
PCT, ng/mL	0.12 (0.08–0.23)	0.3 (0.17–0.78)	0.15 (0.09–0.3)	**<0.001**
PCT >0.5, ng/mL, no (%)	10 (9.9)	14 (34.1)	24 (16.9)	**<0.001**
CT value of PCR, mean (SD)	24.6 (4.9)	23.2 (5.4)	24.2 (5.1)	0.17
Outcomes, median (IQR)				
Admission, no (%)	79 (78.2)	41 (100)	120 (84.5)	**<0.01**
Number of days admitted	3 (2–6)	7 (4–24)	4 (2–8)	**<0.001**
Start of antibiotics, no (%)	25 (24.8)	21 (51.2)	46 (32.4)	**<0.01**

No. of missing values per variable (n): days since onset of symptoms (16), respiratory rate (7), heart rate (3), systolic and diastolic blood pressure (2), use of antibiotics in last 7 days (1), creatinine (1), LDH (9), ferritin (18), lymphocyte count (6), CT value PCR (8).
Statistically significant data is highlighted in bold.
*No adjustment for multiple testing was made.
†Cardiovascular diseases includes i.a. a history of (un)stable angina pectoris, heart rhythm disorder, myocardial infarction, chronic heart failure, peripheral vascular disease.
‡Pulmonary disease includes chronic obstructive pulmonary disease, asthma, cystic fibrosis, obstructive sleep apnoea syndrome or pulmonary hypertension.
§Neurological disease includes cerebral vascular attack, transient ischaemic attack, multiple sclerosis, amyotrophic lateral sclerosis and Parkinson disease.
¶Renal disease includes an eGFR <50 mL/min, proven kidney disease or kidney transplant.
**PSI group 1: 0–50, group 2: 51–70, group 3: 71–90, group 4: 91–130, group 5: 131–395.
CRP, C reactive protein; CT, cycle threshold; eGFR, estimated glomerular filtration rate ; LDH, lactate dehydrogenase; PCT, procalcitonin; PSI, Pneumonia Severity Index; q-SOFA, quick sequential organ failure assessment.

Table 2 Microbiological results of all tests performed within 48 hours of presentation

	Total	Positive	Deemed contaminants
Blood cultures	175	11	11
Sputum cultures	15	1	0
Mycoplasma or *Chlamydia* PCR	2	0	0
Pneumococcal antigen tests	14	1	0
Legionella antigen tests	15	0	0

p<0.001). There was no significant difference in temperature, blood pressure, heart rate or Glasgow Coma Score. In the laboratory findings, patients with a severe disease course had significantly higher levels of creatinine, lactate dehydrogenase, ferritin, CRP and PCT, whereas the lymphocyte count was significantly lower.

In logistic regression analysis, CRP and PCT were both significantly associated with severe disease course, with ORs of 1.8 (unadjusted) and 1.7 and 1.8 (adjusted), respectively (table 3). Lymphocyte count was not significantly associated with severe disease course in our study (OR 0.7 (0.4 to 1.1)). For the different PCT categories and the PSI groups, a higher category resulted in higher odds for severe outcome.

The ROC curve for PCT had an AUC of 0.76 (0.68 to 0.84), CRP showed an AUC of 0.70 (0.61 to 0.79). The AUC of the PSI score was 0.72 (0.63 to 0.81) (table 4). Combining PCT with PSI did not result in an increase in AUC compared with PSI or PCT alone (0.73, 0.64 to 0.82).

To exclude that our findings were driven by the non-severe subgroup of patients with COVID-19 who were not admitted to the hospital (n=22), the analysis was also performed for hospitalised patients only (n=79 non-severe vs n=41 severe). This revealed similar results (see online supplemental table 2 and table 3).

DISCUSSION

We found that in patients with COVID-19 presenting to the ED from whom a blood culture was taken, bacterial coinfection was only present in 1.4% of the patients, which supports a restrictive antibiotic policy. Moreover, blood cultures seem to be of limited value in this setting as no pathogens were detected whereas 6.3% of the blood cultures returned false positive due to contamination. Of all biomarkers investigated, PCT was most discriminative between severe disease course and non-severe disease course compared with CRP, ferritin and lymphocytes. The widely implemented PSI score also performed well compared with these biomarkers.

Table 3 ORs for biomarkers, PSI and severe outcome

	OR	95% CI	Adjusted OR	Adjusted 95% CI
*OR for biomarkers**				
PCT†	1.8	1.3 to 2.3	1.7	1.3 to 2.2
CRP‡	1.8	1.3 to 2.6	1.8	1.3 to 2.6
Lymphocytes‡	0.6	0.3 to 0.9	0.7	0.4 to 1.1
Ferritin‡	1.3	0.99 to 1.8	1.4	1.04 to 1.9
PCT in groups†				
PCT <0.10 ng/mL	Ref	Ref	Ref	Ref
PCT 0.10–0.25 ng/mL	6.2	1.7 to 23	5.5	1.5 to 20.7
PCT 0.25–0.50 ng/mL	11.1	2.4 to 51.6	10.5	2.1 to 52.1
PCT >0.50 ng/mL	20.1	4.8 to 83.4	16	3.8 to 68.4
OR for PSI groups				
PSI group 1	Ref	Ref		
PSI group 2	0.98	0.2 to 4.8		
PSI group 3	3.7	0.9 to 15.2		
PSI group 4	5.5	1.4 to 21.3		
PSI group 5	8.8	1.6 to 47.8		

*The log2 was used, in this way the ORs refer to a doubling in the value of the variable.
†Adjusted for age and severe kidney disease (On dialysis, creatinine >270 µmol/L, uraemia, history of kidney transplant).
‡Adjusted for age.
CRP, C reactive protein; PCT, procalcitonin; PSI, Pneumonia Severity Index.

Table 4 AUC of the ROC curve for biomarkers and severe disease course

	AUC	95% CI
PCT	0.76	0.68 to 0.84
CRP	0.70	0.61 to 0.79
Ferritin	0.62	0.51 to 0.74
Lymphocyte count	0.62	0.51 to 0.72
PSI score	0.72	0.63 to 0.81

AUC, area under the ROC curve; CRP, C reactive protein; PCT, procalcitonin; PSI, Pneumonia Severity Index; ROC, receiver operating characteristics.

A strength of our study is that only patients from whom a blood culture was drawn were included. The low rate of bacterial coinfection is in line with previous studies reporting rates of 0%–8%.[5 6] However, as blood cultures are indicated based on clinical judgement of the attending physician (eg, suspected sepsis), it is likely that a relatively high risk of bacterial coinfection was suspected. Seen in this light, the 1.4% incidence of bacterial pulmonary coinfection is surprisingly low. However, our study population is different than most previous reports, that mostly refer to non-European, hospitalised patients including also non-respiratory infections.[5 6] In addition, in the Dutch healthcare system almost all patients consult their general practitioner before visiting the ED. Consequently, 28% of our population received antibiotics prior to ED presentation, which may have decreased the number of detected bacterial coinfections.

The 6.3% rate of contaminated blood cultures in our study is remarkably high. To interpret this number, we analysed contamination rates of all patients included in the PredictED study who were diagnosed with a respiratory infection before the COVID-19 pandemic. In this period, 2.6% (16/604) of blood cultures were contaminated (data not shown). One could argue that the high work pressure at the ED during the first wave of COVID-19 and the burden of working in protective equipment might have contributed to a higher rate of contamination.

Recently, Karami *et al* reported a bacterial coinfection rate of 1.2% in the first week of hospitalisation in 925 patients. In this study, only four blood cultures were positive while 60 from 711 blood cultures (8.4%) were contaminated.[18] Another retrospective study in the Netherlands among patients with COVID-19 with a blood culture being performed within 48 hours after a positive SARS-CoV-2 PCR test showed a bacteraemia rate of 1% while 8% of blood cultures were contaminated.[19] In a large multicentre study conducted in New York City, the yield of blood cultures in patients with COVID-19 was only 1.6% while another 2.2% was contaminated.[20] This included pathogens indicating non-pulmonary coinfections and blood cultures that were taken either at the ED or during hospitalisation. As in our study, the number of false positive blood cultures exceeded the number of true positives in these studies. Meanwhile, the large numbers of blood cultures overwhelmed the capacity of laboratories. In addition, contamination of blood cultures is associated with a prolonged hospital stay and more antibiotic prescription.[21]

Therefore, we suggest that blood cultures should not be routinely performed in patients with COVID-19 presenting to the ED. Sputum cultures and urinary antigen tests might be a more efficient way to diagnose bacterial coinfection, especially in patients with known underlying pulmonary or immunocompromising comorbidities, as in our study. However, with a yield of 1.4%, our study does not support the routine use of sputum cultures and antigen testing for all patients with COVID-19.

PCT is known as a marker of bacterial infection.[22] In our cohort, PCT levels ranged from 0.02 to 25 ng/mL. Since we found bacterial coinfection in only two patients, this seems to play a limited role in the elevated PCT levels of patients with COVID-19 presenting to the ED. Likely, in absence of bacterial infection, this might reflect systemic inflammation, which is also known to increase PCT levels.[23] This would be consistent with the beneficial effects of corticosteroids in patients with COVID-19 in need of oxygen therapy, which is aimed at tempering host immune response.[24] Because of the limited number of bacterial coinfections, we were not able to investigate the association with PCT value in this population. However, our results suggest that even in patients with elevated PCT levels or a high PSI score, a restrictive antibiotic policy could still be considered. Whether PCT can be used to rule out a bacterial coinfection should be investigated in future studies.

In previous studies, the biomarkers PCT, CRP, ferritin and lymphocyte count were found to be associated with a severe disease course.[3 4] However, to our knowledge, the discriminative ability of these biomarkers has not been compared. Many studies have tried to develop a prediction model for disease course severity in COVID-19. Unfortunately, as illustrated in a systematic review by Wynants *et al*, almost all models were at high risk of bias and thus are not recommended to use in current practice.[25] Only the 4C Mortality Score, which includes CRP as a biomarker, is considered to be promising.[26] Our results may provide guidance when assumptions must be made in developing a prediction model. For instance, it would be of interest to evaluate the added value of PCT in the 4C Mortality Score.

Our study has several limitations. First, it is an observational study in which the treating physician decided whether to perform microbiological tests. Ideally, the rate of bacterial coinfection would be determined by performing a standardised set of tests in all patients. However, bacterial pulmonary coinfection is diagnosed by combining clinical signs and test results, so including the physician's judgement seems reasonable. Second, our definition of bacterial coinfection is based on microbiological test results only, ignoring a potential clinical diagnosis or a negative culture because of antibiotic pre-treatment. Nevertheless, our study underlines the limited value of blood cultures in diagnosing pulmonary coinfection.[7 27] Third, our sample size is relatively small, so our findings should be interpreted with caution. However, our findings are in accordance with other studies with larger sample sizes.[6 18 19] Finally, only patients from whom a blood culture was drawn were included, so we were not able to study patients with COVID-19 who had no blood culture taken at ED. However, it is likely this would only decrease the rate of bacterial coinfection as there was no clinical suspicion.

In conclusion, the rate of bacterial coinfection of patients with COVID-19 presenting to the ED is low, which supports a restrictive antibiotic policy. Blood cultures appear to have limited value while PCT and the PSI appear promising tools in helping physicians recognise patients at risk for severe disease course.

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Competing interests TO reports personal lecture fees from Gilead, outside the submitted work.

Patient consent for publication Not required.

Ethics approval The PredictED study was approved by the Medical Ethics Committee and the Institutional Scientific Review Board (T18-040). Informed consent was waived since it is an observational quality control study without impact upon patients' medical management.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The deidentified participant data that support the findings of this study are available from the corresponding author, upon reasonable request. Email address: a.g.kaal@hagaziekenhuis.nl.

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