Procalcitonin Predicts Intensive Care Unit Admission and Mortality in Patients With A COVID-19 Infection in The Emergency Department

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Abstract

Introduction

Patients with a severe COVID-19 infection often require admission at an intensive care unit (ICU) when they develop acute respiratory distress syndrome (ARDS). Hyperinflammation plays an important role in the development of ARDS in COVID-19. Procalcitonin (PCT) is a biomarker which may be a predictor of hyperinflammation. When patients with COVID-19 are in the emergency department (ED), PCT could be a predictor of severe COVID-19 infection. The goal of this study is to investigate the predictive value of PCT on severe COVID-19 infections in the ED.

Methods

This was a retrospective cohort study including patients with confirmed COVID-19 infection who visited the ED of Erasmus Medical Center in Rotterdam, the Netherlands, between March and December 2020. The primary endpoint was a severe COVID-19 infection, which was defined as patients who required ICU admission, in-hospital mortality and 30-day mortality after hospital discharge. PCT levels were measured during the ED visit. We used logistic regression to calculate the odds ratio (OR) of PCT on a severe COVID-19 infection, adjusting for bacterial coinfections, age, gender and comorbidities.

Results

A total of 332 patients were included in the final analysis of this study, of which 105 patients reached the composite endpoint of a severe COVID-19 infection. PCT showed an unadjusted OR of 4.19 (CI: 2.52-7.69) on a severe COVID-19 infection. Corrected for bacterial coinfection, the OR of PCT was 4.05 (2.45 – 7.41). Adjusted for gender, bacterial coinfection, age and comorbidities, PCT was still an independent predictor of severe COVID-19 infection with an adjusted OR of 3.82 (CI: 2.26-7.48).

Conclusion

PCT is a predictor of severe COVID-19 infections in patients with a COVID-19 infection in the ED. The routine measurement of PCT in patients with a COVID-19 infection in the ED may assist physicians in the clinical decision making process regarding ICU disposition when PCT levels are elevated.

Introduction

Coronavirus disease (COVID-19) caused by the novel Coronavirus (SARS-CoV-2) was declared a pandemic on the 11th of March 2020 by the World Health Organization¹. Ever since, COVID-19 caused a high burden on hospital and intensive care unit capacity². Patients with COVID-19 often require hospitalization and treatment at an intensive care unit (ICU) when they develop acute respiratory distress syndrome (ARDS). The exact underlying pathophysiology of ARDS in these severe COVID-19 infections is under research with an exponentially growing amount of studies on this topic^{3,4}. Many studies have found that hyperinflammation, caused by an overwhelming upregulation of the immune system, and immune thrombosis play a major role in the development of ARDS in COVID-19⁵.

When patients with a COVID-19 infection present at the emergency department (ED), it is important to be able to identify patients who are at high risk of developing a severe COVID-19 infection. These patients may benefit from more extensive monitoring or early ICU admission.

Different biomarkers have been identified as predictors of disease severity in COVID-19⁶, including procalcitonin (PCT). PCT is a biomarker previously used for distinguishing viral infections from bacterial infections⁷, although its use in the ED for this purpose is controversial^{8,9}. Elevated PCT levels are often seen in patients with a bacterial infection. PCT is the prohormone of calcitonin and in a physiological state produced by C-cells of the thyroid gland. During inflammation, PCT is synthesized in all tissues. Bacterial toxins are well known triggers of synthesis of PCT. Other triggers of synthesis include interleukin-6 and tumor necrosis factor alpha (TNF-alpha).^{10,11} High levels of these cytokines have been reported in severe COVID-19 infections¹². For this reason, PCT may also be elevated in a hyperinflammatory state in the absence of a bacterial pathogen. ARDS is clinically the most important severe complication of COVID-19, therefore PCT may be predictive of hyperinflammation and the development of ARDS¹³. This may aid physicians in the ED to identify patients that are at risk of developing ARDS early.

The goal of this study is to investigate the predictive value of PCT on severe COVID-19 infections in the ED.

Methods

In this retrospective single center cohort study we included patients who visited the ED of Erasmus University Medical Center, in Rotterdam, the Netherlands, with a confirmed COVID-19 infection between 1 March 2020 and 31 December 2020. Erasmus University Medical Center is an academic hospital with 40.000 ED visits annually. The institutional review board waived informed consent for the retrospective use of clinical data of COVID-19 patients.

Inclusion and exclusion criteria

Patients were included if they tested positive on COVID-19 positive by PCR test at the day of the ED visit, the reason for ED visit was related to the COVID-19 infection and PCT levels were measured in the ED. Patients were excluded if the PCT levels were measured but invalid (e.g. hemolytic blood samples), if the COVID-19 infection was a secondary finding and not the primary reason for ED visit or when no follow-up data were available due to transfer to another hospital.

Data collection

Patient data including demographics, comorbidities, vital signs and laboratory tests were collected from the electronic patient records. Vital signs including heart rate, arterial oxygen saturation, respiratory rate, temperature and blood pressure were recorded from the time of ED visit. Laboratory testing during the ED visit included hemoglobin, red cell distribution width (RDW), leucocyte count, thrombocytes, total bilirubin, alanine aminotransferase (ALAT), aspartate aminotransferase (ALAT), lactate, D-dimer, C-reactive protein (CRP) and PCT. Patients were followed up for 30 days after hospital discharge. Patient disposition from the ED was categorized into discharge home from the ED, admission to general ward and admission to the ICU.

Mortality data was categorized into in-hospital mortality and mortality at home within 30 days after hospital discharge. To correct for potential bacterial coinfections at ED visit, culture within 48 hour of ED visit were reviewed. If cultures or pneumococcal or legionella antigen tests were positive, patients were classified as bacterial coinfection.

Primary outcome

The primary outcome was a severe COVID-19 infection, defined as patients that were admitted to the ICU and patients that died during 30 days follow-up.

Secondary outcomes

The secondary outcomes of this study were hospital admission, ICU admission and mortality. We calculated odds ratios (ORs) for the primary and secondary outcomes for commonly used cut-off values of PCT of 0.25 ng/mL, 0.5 ng/mL and 1.0 ng/mL.

Procalcitonin measurement

PCT analysis was available as a standard laboratory test in patients who visited the ED with a suspected COVID-19 infection. Blood was collected in a lithium heparin tube and analyzed directly upon arrival in the clinical chemistry laboratory. PCT was measured using E801 Elecsys BRAHMS PCT reagent on a COBAS 8000 (Roche Diagnostics, Switzerland). The PCT values were available to the treating physician during the ED visit.

Statistical analysis

Normally distributed variables were reported as mean with standard deviation (SD), non-normally distributed variables as median with interquartile range (IQR). Multiple imputation was used for handling missing data.

Differences in dichotomous variables between the severe and non-severe COVID-19 infection patients were analyzed with chi-square tests. Differences in continuous variables were analyzed using an independent sample T-test for normally distributed data and a Mann-Whitney-U test for non-normally distributed data.

For the primary outcome, we calculated unadjusted odds ratios of the variables that were significantly different between groups using univariate logistic regression analysis. We calculated adjusted ORs of PCT correcting for only bacterial coinfection and for gender, age bacterial coinfection and comorbidities. We constructed receiver operating characteristic (ROC) graphs and calculated the corresponding area under the curve (AUC) of continuous variables to report the predictive value on severe COVID-19 infection.

We reported PCT as a continuous variable for the primary outcome.

For the secondary outcomes, we used predefined cutoff values of 0.25 ng/mL, 0.5 ng/mL, 1.0 ng/mL of PCT and calculated the unadjusted ORs, the sensitivity, specificity, negative predictive value and positive predictive value on the primary and secondary outcomes of the study.

Statistical analyses were performed using 'R' version 3.6.2. We used the MICE package for multiple imputation of missing data.

Results

Between 1 March 2020 and 31 December 2020, a total of 477 patients visited the ED with a confirmed COVID-19 PCR at the day of the ED visit. Procalcitonin was measured in 339 of these patients. Four patients were excluded due to an invalid procalcitonin measurement, two patients were excluded because the ED visit was not related to the COVID-19 infection and one patient was excluded because there was no follow up data available. A total of 332 patients were included in the final analysis of this study. (Fig. 1) There was missing data in 3% of the data. These missing data were imputed using multiple imputation. The amount of missing data per variable are shown in Supplementary File A.

A total of 105 patients reached the composite endpoint of a severe COVID-19 infection. Of these 105 patients, 44 were admitted to the ICU and 61 patients died. The non-severe COVID-19 infection group consisted of 227 patients, of which 67 were discharged directly from the ED and 158 were discharged from the general ward after an uncomplicated hospital admission. Baseline characteristics of both groups are shown in Table 1. The severe COVID-19 group was significantly older, more often male and had more frequently diabetes mellitus and any form of immunodeficiency as comorbidity. In vital parameters there was a significant difference in heartrate, respiratory rate, oxygen saturation and diastolic blood pressure. In laboratory testing there was a significant difference in PCT, CRP, leukocyte count, RDW, ASAT, ALAT, lactate, D-dimer and creatinine. Patients with a severe COVID-19 infection had more often a bacterial coinfection at the ED.

PCT showed an unadjusted OR of 4.19 (CI: 2.52–7.69) on a severe COVID-19 infection with an AUC of 0.815 (CI: 0.764–0.866). Corrected for bacterial coinfection, PCT remained a significant predictor of severe COVID-19 infection with an adjusted OR of 4.05 (2.45–7.41). Adjusted for gender, bacterial coinfection, age and comorbidities, PCT was still an independent predictor of severe COVID-19 infection with an adjusted OR of 3.74 (CI: 2.23–7.31) (Table 2).

We performed an univariate logistic regression analysis of the continuous variables that significantly differed between the non-severe and severe COVID-19 infection groups. The results of this univariate regression analyses are shown in Table 3.

We tested PCT at different cut-off values on the primary and secondary endpoints as shown in Table 4. We used 0.25 ng/mL, 0.5 ng/mL and 1.0 ng/mL as cut-off points of PCT. On the primary endpoint, the OR of PCT at these cutoff points were respectively 9.76 (CI: 5.79–16.83), 12.12 (CI: 6.61–23.2) and 14.40 (CI: 6.45–36.77). On hospital admission, the OR of PCT was 14.68 (CI: 5.27–61.11) at a cutoff point of 0.25 ng/mL and 22.78 (CI: 4.88–406.11) at a cutoff point of 0.5 ng/mL. Since there were no patients who were discharged home with a PCT of higher than 1.0, we could not calculate the OR of PCT at a cutoff of 1.0. For ICU admission, the OR of PCT at the previously mentioned cutoff points were 5.94 (CI: 3.36–10.79), 7.7 (CI: 4.24–14.2) and 8.93 (CI: 4.42–18.51) respectively. For mortality the ORs were 9.72 (CI: 5.2–19.08), 9.38 (CI: 5.08–17.68) and 7.93 (CI: 3.92–16.29) respectively.

Discussion

In this study we found that PCT is a predictor of the combined outcome of ICU admission and mortality with an OR of 4.19 and when used at a cutoff point of 0.5 ng/mL an OR of 12.12. These findings could help in decision making when patients with a COVID-19 infection are admitted to the hospital. Patients with elevated PCT levels are at risk of a severe COVID-19 infection and may require ICU monitoring or treatment.

These findings support findings of other studies where higher PCT levels were seen in hospitalized COVID-19 patients with severe infections^{14–16}. However, it is clinically important to be able to make an early risk stratification when patients are admitted to the hospital. Only few studies have investigated the use of PCT in the ED in patients with a COVID-19 infection. Nazerian et al. found that PCT was not useful in diagnosing COVID-19 in the ED, but did not investigate if PCT was predictive of disease severity.¹⁷ However, similar results as our study were found by Surme et al. who investigated predictors of ICU admission and mortality and also found that PCT was predictive of the composite outcome of ICU admission and mortality¹⁸.

PCT is primarily used as biomarker for bacterial infections. The findings of this study show a new use for PCT in the specific group of COVID-19 patients as marker of disease severity. Even after correcting for bacterial coinfections, PCT remained an independent predictor of a severe COVID-19 infection. When looking at the pathways of synthesis of PCT¹⁰, it is unsurprising that PCT is highly elevated in severe COVID-19 infections. PCT synthesis is upregulated by different cytokines such as interleukine-6 and TNF-alpha. Because hyperinflammation is shown to be an important factor in progression of COVID-19 infections, the dysregulated immune response may also trigger PCT production⁴. Similar results of elevated PCT levels were found in patients with isolated severe influenza virus infections, which supports the hypothesis that PCT is a marker of hyperinflammation¹⁹.

At different cut-off values, PCT showed a high specificity for the primary and secondary outcomes of this study. On hospital admission, the lowest cut-off value of 0.25 ng/mL resulted in a specificity of 97%. This could be used as tool for hospital disposition decisions because the majority of patients with a PCT above 0.25 ng/mL was admitted to the hospital. Different cut-off values of PCT are recommended in distinguishing bacterial from viral infections, also ranging from 0.25 ng/mL to 1.0 ng/mL²⁰. The cut-off values we used in this study correspond to these cut-off values.

Strengths And Limitations

The large patient population strengthens the findings of this study. Furthermore, the patient population consisted solely of confirmed COVID-19 patients. Therefore, the results are not biased by patients who visited the ED with a suspected COVID-19 infection but were diagnosed with an alternative diagnosis. The results of this study cannot be used for distinguishing a COVID-19 infection from other viral or bacterial infections¹⁷.

A limitation of this study is the retrospective design. Patients were included if PCT was measured in the ED. PCT was only measured in patients where the primary reason of the ED visit was suspected COVID-19 infection. Patients that were initially not suspected of having COVID-19, but were diagnosed with a COVID-19 infection, did not have PCT measured and are therefore not included in this study.

PCT was prospectively measured in the ED and available to the treating physician, along with other routinely measured laboratory tests. PCT levels may have been used in clinical decision making and influenced disposition decisions.

Conclusion

PCT is a predictor of severe COVID-19 infections in patients with a COVID-19 infection in the ED. The routine measurement of PCT in patients with a COVID-19 infection in the ED may assist physicians in the clinical decision making process regarding ICU disposition when PCT levels are elevated. These results should be validated in a larger prospective multicenter cohort.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KTM, SE and HE were involved in the conception or design of the manuscript. KTM,YD and HE did the analysis and interpretation of the data. KTM drafted the manuscript. KTM, SE, HE, EJ, CR, DG, EG and YD were involved in the critical revision of the manuscript and final approval of the manuscript.

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Tables

Table 1
patient characteristics

Patient characteristics		All patients	Non-severe COVID-19 infection	Severe COVID-19 infection	p-value
Demographic data			n = 227	n = 105	
Gender: male	n (%)	191 (57.5)	115 (50.7)	76 (72.4)	< 0.001
Age	mean (SD)	60 (16.4)	58.1 (16.1)	64.9 (16.3)	< 0.001
Comorbidity: pulmonary disease	n (%)	83 (25)	53 (23.8)	29 (27.6)	0.54
Comorbidity: Cardiovascular disease	n (%)	165 (49.7)	115 (50.7)	50 (47.6)	0.691
Comorbidity: Diabetes Mellitus	n (%)	89 (26.8)	49 (21.6)	40 (38.1)	0.002
Comorbidity: Malignancy	n (%)	52 (15.7)	35 (15.4)	17 (16.1)	0.986
Comorbidity: Renal disease	n (%)	55 (16.6)	43 (18.9)	12 (11.4)	0.12
Comorbidity: Auto-immune diseases	n (%)	37 (11.1)	27 (11.9)	10 (9.5)	0.652
Comorbidity: Immunodeficiency	n (%)	63 (19)	53 (23.3)	10 (9.5)	0.005
Vital parameters					
Heartrate	mean (SD)	94.1 (18.4)	91 (17.9)	101 (19.6)	< 0.001
Respiratory rate	mean (SD)	25.2 (9)	24 (8.9)	27 (8.9)	0.001
Oxygen saturation	median (IQR)	95 (94–97)	96 (94–97)	94 (88–96)	< 0.001
Diastolic blood pressure	mean (SD)	79.4 (16)	81 (15.6)	77 (16.2)	0.005
Systolic blood pressure	mean (SD)	134.6 (22.2)	136 (21.8)	135 (23.2)	0.156
Temperature (Celcius)	mean (SD)	37.6 (1)	37.5 (0.9)	37.8 (1.2)	0.288
Laboratory testing					
Procalcitonin (ng/mL)	median (IQR)	0.14 (0.07–0.38)	0.1 (0.06–0.18)	0.47 (0.17–1.46)	< 0.001

Patient characteristics		All patients	Non-severe COVID-19 infection	Severe COVID-19 infection	p-value
CRP (mg/L)	median (IQR)	62 (26–136)	46 (19–93)	141 (67–213)	< 0.001
Leucocyte count	median (IQR)	6.4 (4.8-9)	5.8 (4.4–7.7)	7.7 (6.1–11.1)	< 0.001
Hemoglobin (mmol/L)	mean (SD)	8 (1.3)	8 (1.2)	7.9 (1.5)	0.504
RDW (%)	median (IQR)	13.3 (12.6–14.6)	13.2 (12.5–14.2)	13.9 (12.9–14.6)	0.014
Thrombocytes	median (IQR)	206 (164–265)	205 (167–264)	206 (160–266)	0.851
ASAT (U/L)	median (IQR)	41 (28–61)	36 (27–53)	53 (36–81)	< 0.001
ALAT (U/L)	median (IQR)	28 (19–48)	27 (18–43)	31 (22–53)	0.012
Total bilirubin (umol/L)	median (IQR)	8 (6–11)	8 (6–11)	8 (6–12)	0.976
D-dimer (mg/L)	median (IQR)	1.07 (0.5–2.18)	1 (0.47–1.48)	1.72 (0.71–4.51)	< 0.001
Creatinine (umol/L)	median (IQR)	88 (70–122)	82 (67–110)	111 (83–163)	< 0.001
Lactate (mmol/L)	median (IQR)	1.3 (1-1.8)	1.2 (1-1.7)	1.6 (1.2–2.5)	< 0.001
Outcome data					
Bacterial coinfection	n (%)	37 (11.1)	19 (8.4)	18 (17.1)	0.030
Admission length	median (IQR)	7 (214)	6 (09)	16 (827)	< 0.001
Mortality	n (%)	61 (18.4)	0 (0)	61 (58.1)	< 0.001

Table 2
multivariate analysis PCT adjusted for age, gender and comorbidity

Predictor	Odds Ratio	Confidence interval
Procalcitonin (ng/mL)	3.74	(2.23–7.31)
Bacterial coinfection	1.64	(0.69–3.84)
Gender	1.03	(1.01–3.51)
Age	1.03	(1.01–1.05)
Comorbidity: pulmonary disease	1.57	(0.85–2.90)
Comorbidity: Cardiovascular disease	0.58	(0.3-1.00)
Comorbidity: Diabetes Mellitus	2.36	(1.23–4.59)
Comorbidity: Malignancy	0.87	(0.40–1.84)
Comorbidity: Renal disease	0.35	(0.12–0.91)
Comorbidity: Auto-immune diseases	0.56	(0.19–1.52)
Comorbidity: Immunodeficiency	0.63	(0.24–1.54)

Table 3
univariate analysis

Predictor	Unadjusted odds ratio	Confidence interval
Procalcitonin (ng/mL)	4.19	(2.52–7.69)
Heartrate	1.03	(1.02–1.04)
Age	1.03	(1.01–1.05)
Respiratory rate	1.03	(1.02–1.07)
Diastolic blood pressure	0.98	(0.96–0.99)
CRP (mg/L)	1.01	(1.01–1.02)
Leucocyte count	1.16	(1.1–1.24)
RDW (%)	1.04	(0.95–1.15)
ALAT (U/L)	1.01	(1-1.01)
ASAT (U/L)	1.02	(1.01–1.02)
Lactate (mmol/L)	2.15	(1.56–2.94)
D-dimer (mg/L)	1.22	(1.13–1.4)
Creatinin (umol/L)	1.01	(1-1.01)
Oxygen saturation	0.85	(0.82–0.92)

Table 4
Procalcitonin at different cutoff points on primary and secondary outcomes

Outcome	Cut-off value PCT	Odds ratio	Confidence interval	Sensitivity	Specificity	Negative predictive value	Positive predictive value
Severe outcome	Continuous scale	4.19	(2.52–7.69)				
	0.25 (ng/mL)	9.76	(5.79–16.83)	0.67	0.82	0.84	0.63
	0.5 (ng/mL)	12.12	(6.61–23.2)	0.49	0.92	0.79	0.75
	1 (ng/mL)	14.40	(6.45–36.77)	0.31	0.96	0.75	0.82
Hospital admission	Continuous scale	1667,00	(67.91-98005.22)				
	0.25 (ng/mL)	14.68	(5.27–61.11)	0.40	0.95	0.28	0.97
	0.5 (ng/mL)	22.78	(4.88-406.11)	0.25	0.98	0.25	0.98
	1 (ng/mL)	NA	NA	0.15	1	0.22	1
ICU admission	Continuous scale	1.15	(1.05–1.3)				
	0.25 (ng/mL)	5.94	(3.36–10.79)	0.66	0.74	0.90	0.39
	0.5 (ng/mL)	7.70	(4.24–14.2)	0.53	0.87	0.88	0.50
	1 (ng/mL)	8.93	(4.42–18.51)	0.36	0.93	0.85	0.6
Mortality	Continuous scale	1.22	(1.08–1.43)				
	0.25 (ng/mL)	9.72	(5.2-19.08)	0.75	0.76	0.93	0.41
	0.5 (ng/mL)	9.38	(5.08–17.68)	0.57	0.87	0.90	0.50
	1 (ng/mL)	7.93	(3.92–16.29)	0.36	0.93	0.86	0.55

Figures

Figure 1

Flow diagram of included patients

Supplementary Files

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