



# Procalcitonin accurately predicts mortality but not bacterial infection in COVID-19 patients admitted to intensive care unit

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## Abbreviations

APACHE II	Acute physiology and chronic health evaluation II
AUC	Area under the curve
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
ICU	Intensive care unit
IL	Interleukin
IQR	Interquartile range
PCT	Procalcitonin
ROC	Receiver operating characteristic
RT-PCR	Reverse-transcriptase polymerase-chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOFA	Sequential organ failure assessment
TNF- $\alpha$	Tumour necrosis factor $\alpha$

## Introduction

Procalcitonin (PCT) is used as a biomarker of lower respiratory tract bacterial infection therefore guiding antibiotic therapy in the intensive care unit (ICU) [1].

The prevalence of bacterial co-infections in hospitalized patients with COVID-19 represents less than 10% of cases but is higher in critically ill patients.

Recently, bacterial respiratory infection in critically ill COVID-19 patients was estimated between 14 and 28% [2–4]. However, antimicrobial prescribing has increased since the beginning of the pandemic representing a threat to antimicrobial resistance worldwide [5].

Different studies have shown an association between high PCT values in COVID-19 and increased mortality rates [6].

We aimed to explore the prognostic value of PCT at ICU admission in critically ill COVID-19 patients as well as the relationship between bacterial co-infection and PCT levels within 48 h from ICU admission.

## Materials and methods

### Study design and participants

All adults admitted to the ICU for acute respiratory failure related to SARS-CoV-2 pneumonia (diagnosed by a positive result on real-time reverse-transcription polymerase-chain reaction (RT-PCR) on nasopharyngeal swab) between 3 March 2020 and 2 June 2020 were retrospectively included.

### Data collection

Files were retrospectively reviewed as well as laboratory findings, radiological results and outcome data.

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## PCT measurements

PCT concentrations were measured using Lumipulse G B•R•A•H•M•S PCT Immunoreaction Cartridges on a Lumipulse G600II instrument (Fujirebio, Gent, Belgium).

## Definition of bacterial co-infection

Bacterial co-infection was defined when a patient has a positive culture for a bacterial pathogen obtained from lower respiratory tract collections (sputum, endotracheal aspirate, or bronchoalveolar lavage fluid) or blood samples within 48 h of ICU admission. Detection of bacteria in an isolate not from respiratory tract or blood sample was not selected.

## Statistical analysis

We analysed the relation of PCT value and mortality at 30 days.

Continuous and categorical variables were presented as median (interquartile range, IQR) and *n* (%).

We used univariate tests by chi-square, Fisher exact, Mann-Whitney tests or *t* tests to compare differences between groups according to the characteristics of each variable. Variables that reached a level of significance greater than 0.20 were introduced into a multivariable regression with a forced input of PCT in order to identify the variables independently associated with survival. Collinearity detection tests were carried out.

This study has been approved by the Saint-Pierre University Hospital Ethics Committee (CE-20-07-10).

## Results

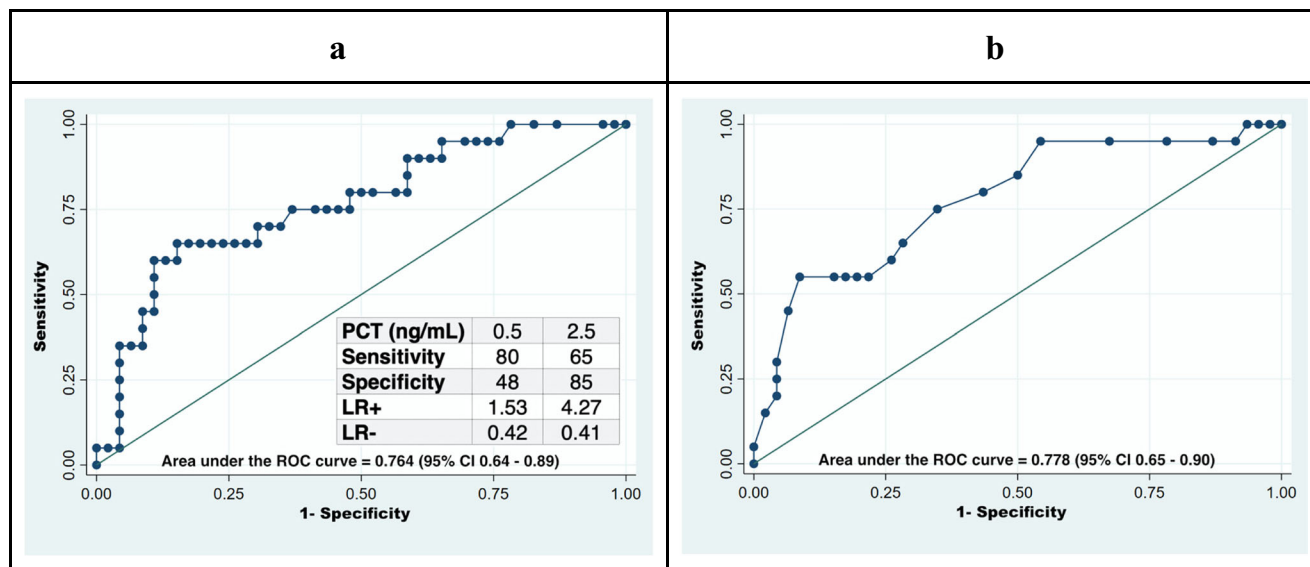
By June 2, 2020, 66 critically ill patients were admitted to the ICU of Saint-Pierre University hospital with confirmed severe SARS-CoV-2 pneumonia (Table 1); 30-day mortality was 30% (20/66).

Median PCT within the first 24 h of admission was 4.22 ng/mL (IQR 0.80–18.10) in the non-survivor group and 0.53 ng/mL (IQR 0.17–1.64,  $p = 0.0004$ ) in the survivor group, respectively. Non-survivors had significantly more frequently PCT levels  $\geq 0.5$  ng/mL than survivors ( $p = 0.023$ ). The area under the curve (AUC) of the receiver operating characteristic (ROC) analysis of PCT to predict 30-day mortality was 0.77 (95% CI, 0.64–0.90) (Fig. 1a), similar to results obtained using the APACHE II (0.78 (95% CI, 0.65–0.90)) (Fig. 1b) and SOFA (0.77 (95% CI, 0.65–0.90)) but higher than CRP (0.66 (95% CI, 0.50–0.82)).

In multivariate analysis, only APACHE II score was significantly associated with death ( $p = 0.044$ ) (Table 2, Supplementary data).

PCT prognostic value at a cut-off of 0.5 ng/mL showed a sensitivity of 80%, a specificity of 48% and a positive likelihood ratio of 1.53. A cut-off of 2.5 ng/mL showed a sensitivity of 65% with a specificity of 85% and positive likelihood ratio of 4.27 (Fig. 1a).

A total of seven (11%) patients were co-infected with bacterial pathogen upon ICU admission. Median PCT levels were not significantly different in patients with (11.8 ng/mL; IQR 0.3–90.3) or without (0.7 ng/mL; IQR 0.3–2.8) co-infection ( $p = 0.14$ ) (Fig. 2, Supplementary data). Co-infection was not associated with increased mortality rate; 5/7 (71%) patients with bacterial co-infection were alive at 30 days upon ICU admission ( $p = 0.89$ ) (Table 3, Supplementary data). The AUC for PCT as a



**Fig. 1** Receiver operating characteristic curve of procalcitonin and APACHE II used to predict 30-day mortality in patients with COVID-2019 on intensive care unit admission. Receiver operating curve to illustrate sensitivity and specificity of PCT (left panel) and APACHE II (right

panel) to predict death at 30 days upon ICU admission. PCT, procalcitonin; APACHE II, Acute Physiology and Chronic Health Evaluation (APACHE) II score, positive likelihood ratio, LR+; negative likelihood ratio, LR-

predictor of bacterial co-infection was 0.68 (95% CI, 0.40–0.95). Using cut-off of PCT  $\geq 0.5$  ng/mL to compare between both resulted in a sensitivity of 71% and a specificity of 43%.

## Discussion

As previously described, we observed in critically ill COVID-19 patients that increased PCT values at admission were associated with an increased risk of mortality [7, 8].

PCT is a prohormone whose secretion by extra-thyroidal tissues is stimulated by inflammatory cytokines and endotoxins but inhibited by IFN- $\gamma$ , leading to a specificity for bacterial infection that is used in antibiotic stewardship decisions in current practice until the SARS-Cov-2 pandemic [1].

Pathogenic inflammation induced by SARS-CoV-2 such as elevated pro-inflammatory markers and cytokines like serum interleukin (IL)-6 and tumour necrosis factor (TNF)- $\alpha$  has been described in up to 20% of severe COVID-19 patients and is associated with clinical deterioration and mortality [7, 9].

Our findings are in line with previous results as higher PCT are associated with higher mortality in the SARS-CoV-2 pneumonia but also in critically ill patients in general [9, 10].

However, APACHE II score, in our analysis, was as reliable as PCT in predicting mortality without incurring in supplementary cost.

Bacterial co-infection in critically ill patients COVID-19 occurred between 14 and 28% of cases according to previous studies [2–4]. Before the COVID-19 pandemic, guidelines and previous trial results discouraged the prescription of antibiotics for patients with PCT values  $\leq 0.1$  ng/mL and strongly recommended antibiotics for patients with PCT values  $\geq 0.5$  ng/mL [1].

In our cohort, withholding antibiotic treatment in patients with PCT levels  $\leq 0.1$  ng/mL would have resulted in not treating none of all patients with proven bacterial infection. Moreover, the routine administration of antibiotics in patients with PCT  $\geq 0.5$  ng/mL resulted in overtreating 34 out of 39 patients (87%). With regard to the median value of PCT in co-infected group, it is difficult to interpret any association given the too small number of patients. Large and conclusive data are needed to clarify the role of PCT to predict the occurrence of bacterial co-infection in critically ill COVID 19 patients.

To our knowledge, it is the first study that aims to explore the role of PCT and its association with bacterial co-infection upon admission to ICU.

Limitations of our study are its retrospective design, small sample size and monocentric design, which might limit its generalisation.

In conclusion, we show that PCT levels at ICU admission in COVID-19 patients are a predictor of mortality as accurate as APACHE II. Meanwhile, PCT is not reliable to diagnose bacterial co-infection within 48 h of admission.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11845-020-02485-z>.

**Authors' contributions** Conceptualization : Ioannis Veliziotis.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## Appendix

**Table 1** Main characteristics, comorbidities, laboratory data performed within 48 h of ICU admission and outcomes of 66 critically ill patients with confirmed SARS-CoV-2 infection

	Survivors (n = 46)	Non- survivors (n = 20)	Total (n = 66)	p value
<b>Demographic information</b>				
Age, years	54.5 (47–65)	72.5 (61–74.5)	61 (49–71)	< 0.001
<b>Sex</b>				
Female	17 (37%)	8 (40%)	25 (38%)	0.815
Male	29 (63%)	12 (60%)	41 (62%)	
<b>Comorbidities</b>				
BMI, kg/m <sup>2</sup>	29 (25–32)	30.5 (27–33)	29.5 (26–32)	0.605
<b>Chronic medical illness</b>				
Hypertension	31 (67%)	14 (70%)	45 (68%)	
Diabetes mellitus <sup>a</sup>	21 (46%)	13 (65%)	34 (51%)	0.148
Chronic obstructive pulmonary disease	16 (35%)	5 (25%)	21 (32%)	0.433
Asthma	1 (2%)	3 (15%)	4 (6%)	0.045
Immunosuppression	2 (4%)	-	2 (3%)	0.344
Malignancy	6 (13%)	2 (10%)	8 (12%)	0.728
Chronic kidney disease <sup>b</sup>	9 (19%)	2 (10%)	11 (17%)	0.338
Cerebrovascular	7 (15%)	3 (16%)	10 (15%)	0.988
<b>Outcomes</b>				
Duration from onset of symptoms to ICU admission, days	2 (4%)	2 (10%)	4 (6%)	0.400
ICU length of stay, days	10 (6–12)	8 (7–10)	9 (7–11)	0.343
<b>Treatments</b>				
Antibiotics	12.5 (4–31)	9 (5–13)	11 (5–26)	0.146
Duration, days	35 (76%)	19 (95%)	54 (81%)	0.067
Antiviral <sup>c</sup>	12 (7–22)	12 (9–17)	12 (8–20)	0.636
Steroids	14 (30%)	6 (30%)	20 (30%)	
Duration, days	12 (26%)	6 (30%)	18 (27%)	0.743
<b>Laboratory and clinical findings</b>				
APACHE II score	7 (5–23)	5 (3–10)	7 (5–13)	0.207
P/F <sup>d</sup>	12 (9–18)	23 (14–25)	17 (8–22)	0.0002
PCT (ng/mL)	100 (84–173)	75 (56–93)	93 (70–136)	0.0023
$\geq 0.5$ ng/mL	0.53 (0.17–1.64)	4.2 (0.80–18.10)	0.88 (0.3–3.5)	0.0004
CRP (mg/L)	23 (50%)	16 (80%)	39 (59%)	0.023
				0.04

**Table 1** (continued)

	Survivors ( <i>n</i> = 46)	Non- survivors ( <i>n</i> = 20)	Total ( <i>n</i> = 66)	<i>p</i> value
Bacterial co-infection ( <i>n</i> ) <sup>c</sup>	136 (106–2- 13)	235 (111–322)	166 (109– 258)	0.885

Data are *n* (%) or median (IQR, interquartile range). *p* values were calculated by  $\chi^2$  test, Mann-Whitney test as appropriate

*BMI* body mass index (calculated as weight in kilograms divided by height in meters squared), *APACHE II* Acute Physiology and Chronic Health Evaluation (APACHE) II score

<sup>a</sup> Based on a diagnosis of diabetes mellitus

<sup>b</sup> Based on a diagnosis of chronic kidney disease in medical history by KDIGO

<sup>c</sup> Antiviral treatment: remdesivir, favipiravir, oseltamivir

<sup>d</sup> PaO<sub>2</sub>/FiO<sub>2</sub>

<sup>e</sup> From respiratory tract or blood culture samples within 48 h upon ICU admission

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