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## Clinical Studies

## Procalcitonin as a biomarker for ventilator associated pneumonia in COVID-19 patients: Is it an useful stewardship tool?

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## ABSTRACT

Ventilator associated pneumonia(VAP) is a severe complication that can lead to high mortality when not early identified or when therapy is delayed. The aim of this study was to evaluate procalcitonin(PCT) as a biomarker for VAP development. In total, 73 hospitalized patients with COVID-19 were analyzed. PCT levels greater than 0.975ng/mL were more related to VAP. No association was found for C-reactive protein (CRP). The results show that procalcitonin may be a pertinent biomarker for VAP diagnosis and can be a helpful tool for antibiotic withdrawal.

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## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic caused by SARS-CoV-2 that already exceeded 30 million confirmed cases (World Health Organization 2020). This virus can cause acute respiratory distress syndrome (ARDS), an acute life-threatening condition characterized by hypoxemia and pulmonary alterations. Mechanical ventilation (MV), extra corporeal membrane oxygenation (ECMO) and prone position are common supportive measures of this disorder. However, MV can lead to ventilator associated pneumonia (VAP), a severe complication which, when not identified early on or when empiric therapy is delayed, represents a threat. VAP is a pulmonary infection that can occur after 48h of MV and is responsible for increasing hospitalization time by 11,5 to 13,1 days (IDSA VAP Guideline, (Kalil et al., 2017)) and, therefore costs (Safdar et al., 2005). The patient's mortality ranges from 20% to 50% (Kalil et al., 2017). The importance of VAP prevention, as well as its early diagnostic, is reinforced in COVID-19 patients due to the immunological and inflammatory profile of severe cases and the prolonged length ICU stay (Póvoa et al., 2020). The clinical features of COVID-19 pneumonia

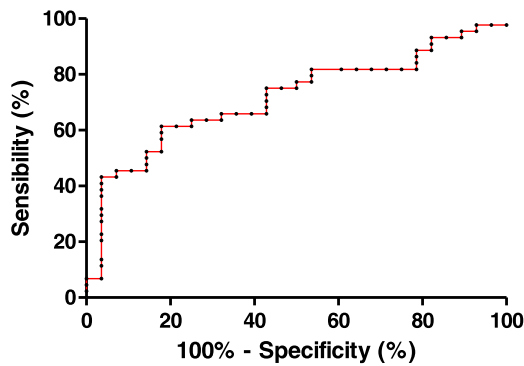
present usually as high fever, severe hypoxemia, hyperleukocytosis, biological inflammatory syndrome and extensive bilateral radiologic alterations. VAP diagnosis in critical COVID-19 patients is a challenge once both share similar symptoms and differential by pulmonary imaging may be challenging. Therefore, usual characteristics for VAP diagnosis are not applicable in critical COVID-19 patients (François et al., 2020). As a result, the urgency of discovering new VAP biomarkers becomes extremely necessary. Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin, involved with calcium homeostasis. PCT is a prohormone synthesized in several tissues. In healthy patients, only the procalcitonin produced in the thyroid has a proper physiological function, participating in calcium homeostasis. In patients with several acute events, mainly infections, it is elevated, and serves as an instrument to assist the risk stratification (Jekarl et al., 2019) of early diagnosis of VAP in hospitalized patients. The aim of this study was to evaluate procalcitonin as a biomarker for VAP development at intensive care units (ICU) ( Fig. 1).

## 2. Methods

Hospital das Clínicas is a tertiary university hospital and the reference center for COVID-19 patients in the state of São Paulo, Brazil.

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**Fig. 1.** ROC curve showing the correlation between VAP diagnosis and PCT levels. AUC 71.7%,  $P=0.002$ . Graphic was designed using GraphPad prism 5.

This study is a cohort involving 73 patients hospitalized between April and June 2020 with a confirmed diagnostic for SARS-CoV-2 by RT-PCR and with a suspected secondary infection. This work was accepted by the research ethics committee; number 4.360.588. Daily visits to discuss ICU cases and the use of antibiotics was conducted by the infection control team of the hospital comprising 8 infectious diseases physicians. The patients were classified as having a secondary healthcare associated infection (HCAI) and VAP using CDC criteria. If the patient met the secondary infection criteria, a PCT sample was collected on day 1 and the other two subsequent days. Antimicrobial treatment was empirically administered based on local data and was discontinued according to the patients clinic and if the PCT value was

less than 0.5 in at least two samples. Endotracheal aspirate and blood cultures were also collected. Data regarding clinical and demographic characteristics, including comorbidities, antibiotics and laboratory tests were collected from electronic medical records. Blood was collected using tube Gel BD Vacutainer SST® (BD, New Jersey, EUA). Tubes were centrifuged at 3000 rpm for 10min and PCT levels were measured in the serum using VIDAS® B.R.A.H.M.S PCT™ (BioMérieux, Marcy l'Etoile, France). Data was analyzed using epiinfo (CDC Epiinfo 7.2) and ROC curve was designed using Graphpad prism 5. Categorical variables were presented as absolute numbers and percentages, and continuous variables as median. Univariable associations between demography and biomarkers levels and VAP were tested. Statistical tests were two tailed, 95% confidence intervals were calculated using the exact binomial method; with a significance level of 0.05.

### 3. Results

A total of 73 patients admitted at ICU with a positive COVID-19 test were analyzed (Table 1). Among these, 28 (38%) evolved with VAP. Gender, age and ethnicity was equally distributed between VAP and non VAP group. The most frequent comorbidity was hypertension (52%) followed by diabetes (35.6%) and obesity (16.4%). Among all exams analyzed, only PCT presented significant difference ( $P=0.0010$ ) between VAP and non-VAP group. Both groups had similar mortality score, Simplified Acute Physiology Score III (SAPS3) and days on MV. The most commonly isolated microorganisms in blood were gram positive with coagulase-negative *staphylococci* being the most frequent, isolated in 23.3% of patients. Gram negative bacteria

**Table 1.** Clinical and demographic characteristics of COVID-19 patients of this study.

	Details	Total (n = 73)	VAP (n = 28)	Non-VAP (n = 45)	P value	RR IC95%
Age	Years	58	59 (25–87)	58 (16–89)	0.83	-
Sex	Female	35 (48%)	12 (42.8%)	23 (51%)	0.25	0.88
	Male	38 (52%)	16 (57.2%)	22 (49%)		
Ethnicity	White	36 (49%)	15 (53.6%)	21 (46.7%)	0.63	1.2
	Black	16 (22%)	5 (17.8%)	11 (24%)	0.57	0.77
	Brown	19 (26%)	7 (25%)	12 (27%)	1	0.96
	Ignored	2 (3%)	1 (3.6%)	1 (2.3%)	1	1.31
Outcome	Death	44 (60.3%)	20 (71.4%)	24 (53.3%)	0.07	1.3
Comorbidities	Hypertension	38 (52%)	15 (53.6%)	23 (51%)	0.42	1.04
	Asthma	1 (1.4%)	0	1 (2.2%)	0.30	0.61
	Diabetes	26 (35.6%)	10 (35.7%)	16 (35.6%)	0.49	1.00
	Obesity	12 (16.4%)	5 (17.8%)	7 (15.5%)	0.39	1.07
	Neoplasm	2 (2.7%)	1 (3.6%)	1 (2.2%)	0.38	1.24
	Neoplasm solid organ	4 (5.5%)	2 (7.1%)	2 (4.4%)	0.33	1.24
	Others	25 (34.2%)	8 (28.6%)	6 (13.3%)	-	-
	None	10 (13.7%)	5 (17.8%)	5 (11.1%)	-	-
	Mortality score	Admission SAPS3	66 (30–101)	67 (30–101)	66 (37–93)	0.93
	Days of MV	21 (3–81)	22 (9–61)	20 (3–81)	0.22	-
Exams	D-dimer (ng/mL)	7517 (685–77,101)	7719 (190–65,626)	7411 (1005–77,101)	0.82	-
	CRP (mg/L)	343 (56–988)	331 (118.8–907)	351 (56–988)	0.82	-
	PCT (ng/mL)	5 (0.06–35.48)	7 (0.13–35.26)	3.8 (0.06–35.4)	0.001	-
	Leucocytes ( $\times 10^3/\text{mm}^3$ )	17,311 (100–95700)	18,090.7 (100–55110)	16,826 (2350–95700)	0.41	-
	Neutrophils ( $\times 10^3/\text{mm}^3$ )	14,926 (1929–83,259)	16,209.4 (5542–50,150)	14,156 (1929–83,259)	0.29	-
	Lymphocytes ( $\times 10^3/\text{mm}^3$ )	1389 (139–6791)	1277.5 (205–6791)	1456 (139–5742)	0.17	-
Gram	Gram +	32 (43.8%)	17 (60.7%)	15 (33.3%)	0.34	1.08
	Gram -	21 (28.8%)	20 (71.4%)	1 (2.2%)	0.03	-
Agents isolated in blood culture	<i>Coagulase-negative staphylococci</i>	16 (22%)	6 (21.4%)	10 (22.2%)	0.47	0.98
	<i>S. aureus</i>	5 (6.8%)	2 (7.1%)	3 (6.7%)	0.46	1.03
	<i>P. aeruginosa</i>	1 (1.4%)	1 (3.6%)	0	0.19	-
	<i>K. pneumoniae</i>	2 (2.7%)	2 (7.1%)	0	0.07	-
	<i>Candida spp.</i>	3 (4.1%)	2 (7.1%)	1 (2.2%)	0.19	1.88
	<i>Enterococcus spp.</i>	3 (4.1%)	2 (7.1%)	1 (2.2%)	0.19	1.88
	Others	45 (61.6%)	19 (67.8%)	26 (57.8%)	0.20	1.17
Antibiotic	Vancomycin	44 (60.3%)	17 (60.7%)	27 (60%)	0.48	1.01
	Piperacillin/Tazobactam	41 (56.2%)	14 (50%)	27 (60%)	0.21	0.85
	Colistin	25 (34.2%)	12 (42.8%)	13 (28.9%)	0.12	1.28
	Others	30 (41%)	14 (50%)	16 (35.5%)	0.12	1.26

VAP = ventilator associated pneumonia.

were significantly more isolated in VAP patients ( $P=0.0003$ ). The most frequently isolated microorganism in blood were Coagulase-negative staphylococci (22%) followed by *S. aureus* (6.8%), *Candida spp.* (4%) and *K. pneumoniae* (2.7%). In tracheal secretion, *P. aeruginosa* was isolated in 6 patients (8.2%) followed by *S. aureus* (6.8%), *A. baumannii* (5.5%) and *K. pneumoniae* (5.5%). The most used antibiotic in general were ceftriaxone (69.8%) followed by meropenem (61.6%), vancomycin (60.3%), piperacillin/tazobactam (56.2%), azithromycin (37%) and colistin (34.2%). In VAP, 67.8% of patients used meropenem, 60.7 % used vancomycin, 50% piperacillin/tazobactam and 42.8% used colistin. Antibiotic treatment was withdrawn in 12% of patients, and it is important to note that the mean PCT values in these patients were significantly lower than those who did not (0.42 ng/mL and 5.72 ng/mL, respectively  $P=0.002$ ). On the other hand, C-reactive protein (CRP) values were not significantly different (295 mg/L and 350 mg/L,  $P=0.21$ ). The ROC curve comparing PCT levels with VAP diagnosis showed that levels of PCT greater than 0.975 ng/mL are more related to VAP with the accuracy of 71.7% ( $P=0.002$ ).

#### 4. Discussion

Here we analyzed clinical data and procalcitonin dosage of 73 COVID-19 hospitalized patients to evaluate PCT as an aid biomarker for VAP diagnosis. Despite the fact that the risk of developing VAP is increased with longer MV, the media of days with MV was a not significantly different between VAP and non-VAP group in this study. Among the exams analyzed in this study, PCT was the only one significantly different from the two groups with a cutoff of 0.975 ng/mL to indicate probable VAP. Indeed, serum PCT levels are increased in bacterial infections so it can be used as a biomarker to differentiate them from viral infections or, in this case, as an indicator of coinfection. Still, based on SEPSIS-3 PCT can be used as a prognostic marker of sepsis and predict mortality in hospitalized patients (Jekarl et al., 2019). In addition, increased PCT levels are associated with higher risk of severe infection in patients with COVID-19 (Lippi and Plebani, 2020). A study involving experts with a background in intensive care medicine and clinical microbiology indicated that VAP diagnosis should be based on chest X-ray, blood cultures, endotracheal aspirate, CRP or PCT, and gram stain. Additionally, the authors indicated PCT as the biomarker with most impact on patient outcomes (Ferreira-Coimbra et al., 2020). In this study, PCT values were also positively associated to antibiotic withdrawal ( $P=0.002$ ), while CRP levels did not ( $P=0.21$ ). Nevertheless, more studies are needed to assess the usefulness of PCT for withdrawal of antibiotics. No differences in the classes of antibiotic prescription was significantly found. Ceftriaxone and azithromycin were not analyzed once they are not antibiotics used to treat VAP. The increase in the use of antibiotics during COVID-19 pandemic is worrying because it can stimulate bacterial resistance even more (Cantón et al., 2020). Indeed, PCT dosage in combination with a rapid multiplex PCR respiratory panel can optimize the use of antibiotic in patients with severe acute respiratory infection preventing antibiotic resistance and misuse and therefore avoiding additional costs (Lee et al., 2020). As stewardship during the pandemic it has been recommending to not use antibiotic prophylactically and to descaled and stop antibiotic as soon as possible. This further emphasizes the importance of finding reliable markers to ensure antibiotic prevention and withdrawal. This study has limitation as be unicentric, the limited size of population and that PCT was not available to COVID patients without a suspect secondary infection.

In conclusion, procalcitonin seems to be a pertinent biomarker for VAP diagnosis and can be a helpful tool for antibiotic withdrawal. Therefore, PCT measurement may indeed play a role in the prognosis of severe COVID-19.

#### Authors' contributions

Marina Farrel Côrtes, conception of the work, analysis, interpretation of data, writing and revising; Bianca Leal de Almeida, conception of the work, writing and revising; Evelyn Patricia Sanchez Espinoza, conception of the work, analysis, writing and revising; Alea Faustina Campos, conception of the work; Maria Luiza do Nascimento Moura, Acquisition of data Matias C. Salomão2, Acquisition of data; Icaro Boszczvoski, Acquisition of data; Maristela Pinheiro Freire, Acquisition of data; Laina Bubach de Carvalho, Acquisition of data; Glauca Paranhos Baccala, Acquisition of data, writing and revising; Silvia Figueiredo Costa, study design, acquisition of data, writing, and revising; Thaís Guimarães, study design, acquisition of data and revising.

#### Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest to declare.

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