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Negative predictive value of procalcitonin to rule out bacterial respiratory co-infection in critical covid-19 patients☆

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SUMMARY

Background: : Procalcitonin (PCT) and C-Reactive Protein (CRP) are useful biomarkers to differentiate bacterial from viral or fungal infections, although the association between them and co-infection or mortality in COVID-19 remains unclear.

Methods: : The study represents a retrospective cohort study of patients admitted for COVID-19 pneumonia to 84 ICUs from ten countries between (March 2020-January 2021). Primary outcome was to determine whether PCT or CRP at admission could predict community-acquired bacterial respiratory co-infection (BC) and its added clinical value by determining the best discriminating cut-off values. Sec-

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ondary outcome was to investigate its association with mortality. To evaluate the main outcome, a binary logistic regression was performed. The area under the curve evaluated diagnostic performance for BC prediction.

Results: : 4635 patients were included, 7.6% fulfilled BC diagnosis. PCT (0.25[IQR 0.1-0.7] versus 0.20[IQR 0.1-0.5]ng/mL, p<0.001) and CRP (14.8[IQR 8.2-23.8] versus 13.3 [7-21.7]mg/dL, p=0.01) were higher in BC group. Neither PCT nor CRP were independently associated with BC and both had a poor ability to predict BC (AUC for PCT 0.56, for CRP 0.54). Baseline values of PCT<0.3ng/mL, could be helpful to rule out BC (negative predictive value 91.1%) and PCT≥0.50ng/mL was associated with ICU mortality (OR 1.5,p<0.001).

Conclusions: : These biomarkers at ICU admission led to a poor ability to predict BC among patients with COVID-19 pneumonia. Baseline values of PCT<0.3ng/mL may be useful to rule out BC, providing clinicians a valuable tool to guide antibiotic stewardship and allowing the unjustified overuse of antibiotics observed during the pandemic, additionally PCT≥0.50ng/mL might predict worsening outcomes.

Introdution

The ongoing pandemic of COVID-19 disease caused by SARS-CoV-2 has overwhelmed healthcare systems and continues to be responsible for a high case-fatality rate in hospitalized patients worldwide. In this regard influenza virus infection has been studied most extensively. In severe influenza H1N1pdm09 pneumonia, the incidence of co-infection has been reported high, ranging from 20-30% [1,2] and its presence has been associated with the severity of illness, worse outcomes, and even with an increased risk of mortality [1,3]. Unlike severe influenza, the incidence of bacterial co-infection in COVID-19 patients admitted to the intensive care unit (ICU) has been observed at a rate of 8%, which is considerably lower than expected at the beginning of the pandemic [4,5].

While there is no scientific consensus on the impact of co-infection on mortality in COVID-19 disease [6,7], it is well known that it leads to worse outcomes, a demand in ICU admission and longer hospital length of stay (LOS) and, consequently, has led to a higher consumption of medical resources [8,9]. Current guidelines advocate using empirical antibiotics for COVID-19 patients under mechanical ventilation [10], which have led to substantial antimicrobial use as high as 80% [4], despite the low described incidence of co-infection. Identifying community-acquired bacterial co-infection among patients with COVID-19 remain a challenge; however, the broad administration of antibiotics is not justified since overuse and wrong consumption of antibiotics could result in fatal effects for the patient and an increase in antimicrobial resistance.

Using biomarkers, could allow higher feasibility for the detection of bacterial co-infections. Procalcitonin (PCT) is a well-known biomarker used clinically and which can be potentially used to differentiate bacterial from viral or fungal infections considering bacterial infections typically show higher PCT serum concentration in recent evidence and serves as a valuable tool in guiding the initiation of antibiotic treatment [11]. In influenza pneumonia, the role of PCT in the early recognition of bacterial co-infection has been widely demonstrated [12]. Conversely, in COVID-19 patients, several studies have shown the association of PCT with the severity of illness [13,14], however, limited data are available that have investigated the role of PCT or C-reactive protein (CRP) in identifying co-infection.

Therefore, the main objectives of our study are to determine the clinical value of PCT or CRP at ICU admission to identify bacterial co-infection in patients with COVID-19 pneumonia. Secondarily, to evaluate its role as definite indicators of prognosis.

Materials and methods

Study design and patients

This is a retrospective study that used prospectively collected data of individuals with severe COVID-19 consecutively admitted to 84 participating ICUs from ten countries (Colombia, Chile, Ecuador, Mexico, Argentina, Uruguay, Brazil, Spain, Ireland, and Andorra) between March 2020 and January 2021. Patients from American countries were included in the LIVEN COVID-19 registry (created by the Latin American Intensive Care Network). Patients from Europe were included in the COVID-19 SEMICYUC database (created by the Spanish Society of Intensive Care Medicine and Coronary Units; NCT04948242). The study was approved by the institutional ethics committee board of the Clínica Universidad de La Sabana (IRB#2020AN28) and Hospital Universitari Joan XXIII (IRB#CEIM/066/2020). The ethics review boards at all other participating centers approved the study protocol. All data were de-identified, allowing the waiver of informed consent. The study protocol followed Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

The inclusion criteria were adults aged older than 18 years admitted to the ICU with the diagnosis of pneumonia and acute respiratory failure due to SARS-CoV-2 infection. A COVID-19 pneumonia diagnosis required a confirmed by the positivity of a reverse transcriptase-polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 from the upper or lower (if the patients were under invasive mechanical ventilation) respiratory tract samples and the presence of a clinical syndrome of severe pneumonia along with pulmonary infiltrates on the chest radiograph [15].

Community-acquired bacterial co-infection was defined as any respiratory bacterial infection diagnosed within 48 hours of hospital admission with the isolation of at least one respiratory pathogen in the blood or a good quality respiratory sample (sputum, tracheal aspirate, or bronchoalveolar lavage) and/or positive urinary antigens for *Streptococcus pneumoniae* or *Legionella pneumophila* [3]. Infections occurring later (> 48 h of ICU admission) were considered as nosocomial infection and not included in the present analysis. Co-infection had to be laboratory confirmed using the Centres for Disease Control and Prevention criteria.

Patients were then classified according to whether or not the diagnosis of bacterial co-infection was met. For the current analysis, the exclusion criteria were: 1) individuals without pneumonia, 2) cases with missing data either on PCT and/or CRP serum levels at admission and 3) patients with missing data on survival and mortality in ICU.

Shock was defined in accordance with the Surviving Sepsis Campaign guidelines [16]; that is, patients in whom adequate fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability. Acute Kidney injury (AKI) was defined according to Consensus Conference of the Acute Dialysis Quality Initiative [17]. Acute respiratory distress syndrome (ARDS) was defined according Berlin definition [18].

Data collection

A case report form was used for data collection by attending clinicians. After anonymizing the data, two experienced investi-

gators checked the recorded information to ensure data accuracy and integrity before validating each database. Extracted data included demographic characteristics (age, gender, and body mass index), underlying medical conditions, the time course of the disease (dates of the illness onset, diagnosis, hospital admission, and ICU admission), laboratory data, microbiologic cultures, radiological findings, respiratory support (non-invasive and invasive), complications and organ failures, treatments, and outcomes. Illness severity was defined at 24 hours of ICU admission using both the Acute Physiology and Chronic Health Evaluation (APACHE) II score [19] and the Sequential Organ Failure Assessment (SOFA) score [20].

PCT and CRP levels at admission were considered the highest level reached by these biomarkers in the first 24 hours of ICU admission. PCT and CRP measurements were performed in local laboratories as a part of routine care. PCT was measured using the Brahms PCT automated immunoassays with a limit of detection of 0.05 mcg/L. The quantitative PCT assays use the "sandwich ELISA" principle to quantify procalcitonin levels by forming antibody–procalcitonin–antibody complexes. CRP was measured using a standardized scattering turbidimetric assay from different manufactures in each center. CRP in a reference population is heavily skewed towards the detection limits of even highly sensitive assays. The quoted upper reference limits vary depending on the assay, but they are typically between 3 and 10 mg/L. Blood samples for cultures and serologic studies were collected routinely at ICU admission. The microbiologic criteria for the etiological cause of co-infection were established when isolated pathogens from respiratory samples accomplished the significant thresholds of the quantitative cultures (growth of bacteria of 10^5 and 10^4 colony-forming units/mL for tracheal aspirate and bronchoalveolar lavage, respectively) [21]. Among non-ventilated patients, good quality of the sputum (purulent sputum with less than ten epithelial cells/100X field and $>$ 25 leukocytes/100 per field) was requested to consider co-infection diagnosis. Culture results were excluded if they were thought to represent contamination or colonization.

Outcomes

The primary outcome was to investigate whether PCT or CRP serum levels on admission could predict bacterial co-infection among patients with COVID-19 pneumonia. The secondary outcome was to evaluate the association of PCT and CRP levels and ICU mortality.

Statistical analysis

No statistical sample size was calculated, and the sample size was equal to the number of patients included in the database during the study period. Corresponding data was reported as percentages for categorical variables and median with interquartile range (IQR) for quantitative variables. Differences between variables were assessed by the chi-squared test (categorical) and Mann–Whitney rank-sum test (quantitative).

A multivariate analysis through binary logistic regression was carried out to study the association of biomarkers and co-infection. To evaluate the diagnostic test performance of biomarkers in predicting co-infection, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristic (ROC) with area under the curve (AUC) were calculated and compared. We performed these analyses using PCT cut-off values of 0.25 and 0.5 ng/mL according to the PRORATA trial [11], besides different clinical significance thresholds to determine the optimal value. Moreover, a CHAID (Chi-Squared Automatic Interaction Detection) decision-tree analysis was modeled to evaluate if PCT and/or CRP could predict bacterial co-infection. CHAID decision trees are nonparametric tools with no assumptions about the data. It is also an exploratory method to investigate the relationship between a dependent variable and a series of predictors. Unlike linear models, they map non-linear relationships with the dependent variable. In our study, bacterial co-infection was the dependent variable, and clinical factors upon ICU admission with significant differences between the co-infection and the non-co-infection group were included in the model as independent variables.

A binary logistic regression analysis was performed to study whether PCT and CRP levels were associated with ICU mortality. PCT and CRP values were included in the model as dichotomous variables. Thus, the PCT threshold was set at 0.50 ng/mL, based on the laboratory-defined reference range. For CRP, the normal reference value (1 mg/dL) was exceeded by 97.2% in our cohort; hence we used the average value of CRP, which corresponded to 15 mg/dl. The selection of variables included in the multivariate model was those with statistical significance in the univariate analysis and those with clinical relevance. Results of the regression coefficients were expressed as odds ratios (OR) with 95% confidence intervals (CI). A p-value <0.05 denoted statistical significance. Data analyses were done with SPSS v.24 (IBM Corp. Armonk, NY, USA).

Results

A total of 7134 patients with confirmed COVID-19 infection were recruited. Among them, 28 patients were excluded because they were not diagnosed with pneumonia, and 2741 were excluded due to missing data. The final study population was 4365 patients, 331 (7.6%) with bacterial co-infection (BC) and 4034 without co-infection (Figure 1).

The main baseline characteristics of the cohort are shown in Table 1. Overall, the median age was 64 years (IQR 55-71), and most of the patients were men (70.6%). The median APACHE II and SOFA scores were 13 (IQR 10-17) and 4 (IQR 3-7), respectively. Hypertension (n= 2020, 46.3%) and obesity (n= 1583, 36.3%) were the most common underlying diseases. The median arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) ratio was 121 (IQR 87-175) mmHg, and 3334 (76.4%) patients required mechanical ventilation during admission. Shock was observed in 1425 (32.6%) patients at admission, and 1108 (25.4%) patients suffered acute kidney injury. The time between the onset of symptoms and hospital admission was 6 (IQR 4-8) days and the time since hospital arrival to ICU admission was 1 (IQR 0-3) day. Hence, the biomarker levels corresponded to the first 48 hours of hospital admission, in the acute phase of the disease, when the co-infection occurs.

Comparison of bacterial co-infection and non-co-infection groups

Patients with BC had higher illness severity scores compared with those without BC, measured by APACHE II (14 [IQR 11-18] versus 13 [IQR 10-17], $p = 0.001$) and SOFA score (5 [IQR 4-8] versus 4 [IQR 3-7], $p < 0.001$). Subjects with BC had higher incidence of hypertension (54.7% versus 45.6%, $p = 0.003$), diabetes (30.2% versus 22.6%, $p = 0.002$), chronic obstructive pulmonary disease (10.9% versus 7.4%, $p = 0.02$) and hematological disease (5.4% versus 3.1%). Since hospital arrival, patients with BC were admitted earlier to the ICU in comparison with those without co-infection (median 1 [IQR 0-3] versus 2 [IQR 0-4] days; $p = 0.001$). Also, patients with co-infection needed more frequently invasive mechanical ventilation (89.4% versus 75.3%, $p < 0.001$), were more likely to develop acute kidney injury (32.3% versus 24.8%, $p = 0.004$), had longer ICU length of stay (21 [IQR 12-37] versus 14 [IQR 8-27], p

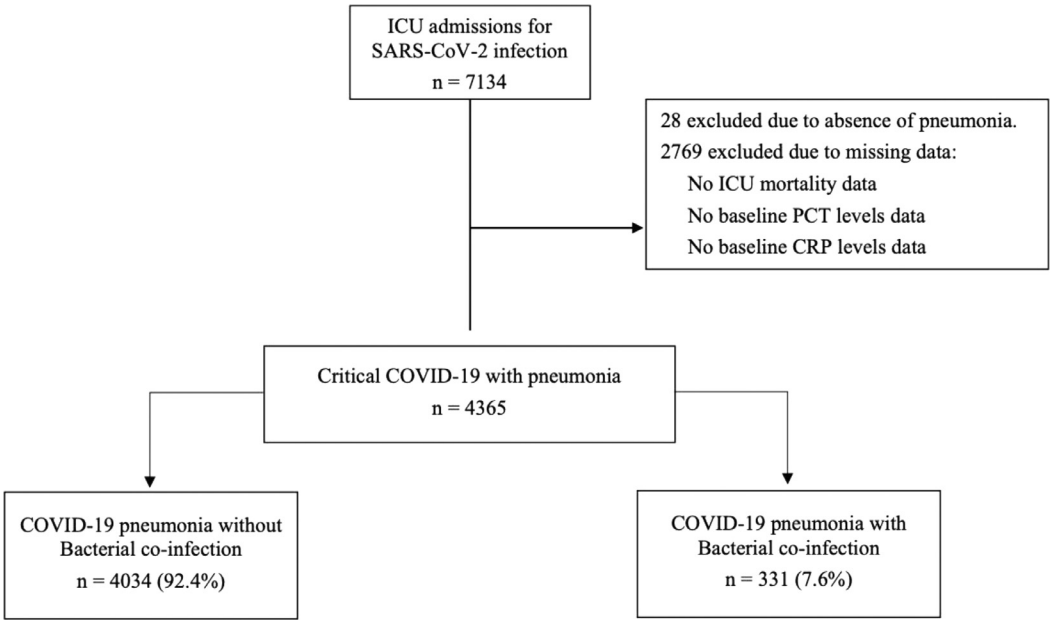

Figure 1. Flow chart of patient enrolment. ICU, Intensive Care Unit; PCT, procalcitonin; CRP, C-Reactive protein.

< 0.001) and higher ICU mortality (37.5% versus 28.9%, p = 0.002). Notably, antibiotic prescription was equally high in both groups.

The most frequently isolated bacterial pathogen in respiratory samples was Methicillin-Susceptible *Staphylococcus Aureus* (MSSA) (19.9%), followed by *Pseudomonas aeruginosa* (18.1%) and *Streptococcus pneumoniae* (17.5%). Causative microorganisms of bacterial co-infection are detailed in Table 1 in the supplementary material.

Diagnostic ability of PCT and CRP as predictors of bacterial co-infection

In the univariate analysis, median values of PCT (0.25 [IQR 0.1-0.7] versus 0.20 [IQR 0.1-0.5] ng/mL, p < 0.001) and CRP (14.8 [IQR 8.2-23.8] versus 13.3 [7-21.7] mg/dL, p = 0.01) were significantly higher in the bacterial co-infection group. Nevertheless, neither biomarker was independently associated with co-infection in the multivariate logistic regression analysis. The only factor independently associated with bacterial co-infection was the presence of a hematological disease (OR 1.69, 95% CI 1.01-2.83, p = 0.04) (Table 2). Moreover, the corresponding receiver operating characteristic (ROC) curve analysis was performed to study whether biomarkers could predict the presence of bacterial co-infection at admission in patients with COVID-19 pneumonia. The ROC curve analysis confirmed the poor ability of both biomarkers in identifying BC, with an AUC of 0.56 (95% CI, 0.53-0.59) for PCT and an AUC of 0.54 (95% CI, 0.51-0.57) for CRP (Figure 1, supplementary material). When applying different cut-off points of PCT levels (not for CRP because of poorer model based on its AUC), we observed that PCT values at admission < 0.3 ng/mL could be a valuable threshold to exclude bacterial co-infection, with a high NPV of 91.1% (95% CI 90.0-92.2). In our cohort, not even higher PCT values presented acceptable PPV, to predict the presence of BC (Table 2, supplementary material). Lastly, the CHAID decision tree analysis confirmed our previous results, as neither of the biomarkers was decisive variables related to bacterial co-infection (figure 2, supplementary material).

Prognostic value of PCT and CRP as predictors of mortality

The overall ICU mortality was 29.5% (n = 1288). Deceased patients were older, had more comorbidities, had higher severity scores, and developed more complications than survivors. Notably, PCT and CRP values, white blood cells count, and D-dimer were significantly higher among non-survivors (Table 3, supplementary material). In the multivariable logistic regression analysis, PCT ≥ 0.50 ng/mL was independently associated with ICU mortality (OR 1.5, CI 95% 1.18-1.84; p <0.001). CRP and bacterial co-infection were not factors associated with mortality. The other factors independently associated with mortality are shown in Table 3.

Discussion

The main finding of this study was that initial PCT and CRP levels did not have a suitable ability to predict community-acquired respiratory co-infection among ICU patients with COVID-19 pneumonia. The main application of PCT could be its ability to exclude at admission a bacterial co-infection when a cut-off <0.30 ng/mL was applied, corresponding with NPV>90%. Furthermore, elevated PCT levels at admission was independently associated with higher mortality, as opposed to CRP values.

In our cohort, the incidence of bacterial co-infection was 7.6%. Previous studies have reported similar low incidence [4,22,23]. Moreover, we did not find an association between bacterial co-infection and mortality, although some studies have shown different results in this regard. Mussuuza et al. [6] carried out a systematic review of 118 studies, finding that co-infection was associated with an almost three times higher risk of death (OR = 2.84; 95% CI 1.42–5.66). However, in this meta-analysis, most of the studies were conducted in a case-mixed setting (ward and ICU) with few critical patients involved and including up to 27% of the pediatric population, making it difficult to compare with our results observed in a more homogeneous cohort. Furthermore, some studies did not clearly state differences between bacterial co-infection and superinfection when reporting the results [9,24]. Although we did not find a significant association of co-infection and mortality, the presence of bacterial co-infection led to more prolonged ICU and hospital length of stay along with longer duration of mechanical ventilation, yielding higher use of healthcare resources, as seen consistently reported in previous data [8,9].

The most frequent isolated pathogen causing co-infection was the methicillin-sensitive S. aureus. It is noteworthy to note that the

Table 1
Baseline characteristics of COVID-19 patients with pneumonia admitted in ICU, and comparison between bacterial co-infection and non-co-infection groups.

	COVID-19 pneumonia(n=4365)	Bacterial co-infection(n=331)	No bacterial co-infection (n=4034)	P value
General characteristics				
Age (years)	64 (55-71)	65 (56-71)	63 (54-71)	0.08
Gender (male)	3080 (70.6%)	246 (74.3%)	2834 (70.3%)	0.12
BMI (kg/m^2)	28 (26-32)	29.1 (26-32.4)	28.5 (26-32)	0.41
Comorbidities				
Hypertension	2020 (46.3%)	181 (54.7%)	1839 (45.6%)	0.003
Obesity (>30 Kg/m^2)	1583 (36.3%)	135 (40.8%)	1448 (35.9%)	0.20
Diabetes mellitus	1012 (23.2%)	100 (30.2%)	912 (22.6%)	0.002
COPD	333 (7.6%)	36 (10.9%)	297 (7.4%)	0.02
Asthma	284 (6.5%)	25 (7.6%)	259 (6.4%)	0.46
Ischemic heart disease	273 (6.3%)	28 (8.5%)	245 (6.1%)	0.08
Immunosuppression	242 (5.5%)	19 (5.7%)	223 (5.5%)	0.89
Chronic kidney disease	218 (5%)	19 (5.7%)	199 (4.9%)	0.52
Chronic heart failure	138 (3.2%)	14 (4.2%)	124 (3.1%)	0.25
Haematological disease	145 (3.3%)	18 (5.4%)	127 (3.1%)	0.03
Course and Severity of illness				
APACHE II score[a]	13 (10-17)	14 (11-18)	13 (10-17)	0.001
SOFA score[b]	4 (3-7)	5 (4-8)	4 (3-7)	< 0.001
PaO_2/FiO_2 (mmHg)[c]	121 (87-175)	120 (84-177)	122 (87-174)	0.95
ARDS	3002 (68.8%)	237 (71.6%)	2765 (68.5%)	0.10
ICU gap	2 (0-4)	1 (0-3)	2 (0-4)	0.001
Laboratory data[c]				
White blood cells count (10^9/ml)	8.9 (6.3-12.8)	9.1 (6-13.5)	8.9 (6.4-12.7)	0.94
C-reactive protein (mg/dl)	13.4 (7-22)	14.8 (8.2-23.8)	13.3 (7-21.7)	0.01
Procalcitonin (ng/ml)	0.2 (0.1-0.5)	0.25 (0.1-0.7)	0.2 (0.1-0.5)	< 0.001
D-dimer (ng/ml)	1000 (592-2210)	1070 (644-2147)	1000 (590-2230)	0.42
Organ failure and complications				
Mechanical ventilation at admission [c]	1853 (42.5%)	158 (47.7%)	1695 (42%)	0.04
Invasive mechanical ventilation	3334 (76.4%)	296 (89.4%)	3038 (75.3%)	< 0.001
Shock [c]	1425 (32.6%)	113 (34.1%)	1312 (32.5%)	0.67
Acute kidney injury [c]	1108 (25.4%)	107 (32.3%)	1001 (24.8%)	0.004
Myocardial dysfunction [c]	386 (8.8%)	25 (7.6%)	361 (8.9%)	0.40
Treatments [c]				
Antibiotics	3523 (80.7%)	278 (84%)	3245 (80.4%)	0.47
Corticosteroids	3346 (76.7%)	260 (78.5%)	3086 (76.5%)	0.4
Tocilizumab	846 (19.4%)	45 (13.6%)	801 (19.9%)	0.006
Remdesivir	337 (7.7%)	26 (7.8%)	311 (7.7%)	0.34
Outcomes				
ICU LOS (days)	15 (8-28)	21 (12-37)	14 (8-27)	< 0.001
Hospital LOS (days)	26 (16-41)	30 (19-49)	25 (16-40)	< 0.001
ICU mortality	1288 (29.5%)	124 (37.5%)	1164 (28.9%)	0.002
Hospital mortality	1365 (31.3%)	131 (39.6%)	1234 (30.6%)	0.001
Duration of MV (days)	15 (8-27)	19 (11-33)	15 (8-27)	< 0.001

Data are expressed as numbers (%) or medians (IQR). Haematological disease included acute leukaemia, myelodysplastic syndrome and lymphomas. ICU gap is the time between hospital admission and ICU admission.
[c] at admission.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Assessment Failure; PaO_2/FiO_2, arterial oxygen partial pressure to fractional inspired oxygen ratio; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation.
[a] Calculated as the worst value within the first 24 hours of ICU admission. [b] Calculated within the first 24 hours of ICU admission.

high incidence of *P. aeruginosa* has been shown to be representative of a causative microorganism of co-infection in these patients. These findings coincide with the results observed by some investigators [25]. In fact, this high incidence of *P. aeruginosa* co-infection has also been reported among critically ill patients with other viral infections such as severe influenza [26]. However, it is uncertain if the broadly administration of empirical antibiotics, corticosteroids and other immunomodulatory agents used against the COVID-19, could partly facilitate the respiratory co-infection of *P aeruginosa* among critically ill patients. The explanation of this high incidence of *P. aeruginosa* in patients with community acquired respiratory co-infection requires further investigation.

Despite the low incidence of co-infection, the consumption of antibiotics on admission was as high as 80.7%. Since the pandemic began, this broad use of empirical antibiotics amongst COVID-19 hospitalized patients has been common practice [4]. Nonetheless, the indiscriminate use of antibiotics is not justified, even in a pandemic. Numerous efforts have been made to predict the presence of bacterial co-infection in patients with SARS-CoV-2 pneumonia at hospital admission in order to better guide the initial treatment with antibiotics and also to predict the evolution of the disease and how it leads to worsening outcomes. Consequently, it has been suggested that some biomarkers may be helpful for this purpose. Our study investigated the most common biomarkers used in routine clinical care. PCT and CRP levels were higher in the bacterial co-infection group, although these biomarkers were not independently associated with co-infection; hence it can be argued that PCT and CRP could not adequately predict bacterial co-infection.

Table 2
Logistic regression analysis for factors associated with the development of bacterial co-infection.

	OR	95% Confidence interval	*P* value
Hypertension	1.26	0.98-1.61	0.07
Diabetes mellitus	1.26	0.97-1.64	0.09
COPD	1.35	0.93-1.97	0.12
Haematological disease	**1.69**	**1.01-2.83**	**0.04**
APACHE II score	1.01	0.99-1.03	0.37
ICU GAP	1.00	0.99-1.00	0.92
Invasive mechanical ventilation	1.15	0.90-1.46	0.26
Acute kidney injury [a]	1.22	0.94-1.58	0.14
CRP [a]	1.01	0.99-1.02	0.12
PCT [a]	1.00	0.99-1.01	0.25

Haematological disease included acute leukaemia, myelodysplastic syndrome and lymphomas.
[a] At admission. COPD: Chronic Pulmonary Obstructive Disease; APACHE: Acute Physiology and Chronic Health Evaluation; ICU GAP: time between hospital to ICU admission in days; PCT: procalcitonin; CRP: C-Reactive Protein.

Table 3
Logistic regression analysis for risk factors associated with ICU mortality in the whole cohort with COVID-19 pneumonia.

	OR	95% Confidence interval	*P* value
Age	1.05	1.04-1.06	<0.001
Gender (Male)	1.10	0.88-1.36	0.38
Hypertension	0.98	0.79-1.21	0.87
Diabetes mellitus	1.00	0.80-1.25	0.98
COPD	1.17	0.84-1.64	0.33
Ischemic heart disease	1.46	1.02-2.09	0.03
Immunosuppression	1.50	1.03-2.18	0.03
Chronic kidney disease	1.16	0.77-1.75	0.46
Chronic heart failure	1.62	0.98-2.67	0.06
Haematological disease	1.88	1.17-3.01	0.01
APACHE II score	1.01	1.00-1.03	0.04
PaO_2/FiO_2 (mmHg) [a]	0.99	0.98-0.99	<0.001
White blood cells count (10^9/ml)	1.00	0.98-1.01	0.98
CRP >15 mg/dL [a]	1.02	0.83-1.24	0.82
PCT >0.5 ng/mL [a]	1.48	1.18-1.84	<0.001
Dimer-D (ng/ml) [a]	1.00	1.00-1.01	0.03
Invasive mechanical ventilation	7.02	4.43-11.10	<0.001
Shock [a]	1.03	0.84-1.26	0.74
Acute kidney injury [a]	2.98	2.43-3.67	<0.001
Myocardial dysfunction [a]	2.25	1.66-3.03	<0.001
Bacterial co-infection [a]	1.21	0.87-1.68	0.24

Haematological disease included acute leukaemia, myelodysplastic syndrome and lymphomas.
[a] At admission. COPD: Chronic Pulmonary Obstructive Disease; APACHE: Acute Physiology and Chronic Health Evaluation; PaO_2/FiO_2, arterial oxygen partial pressure to fractional inspired oxygen ratio; CRP: C-Reactive Protein; PCT: procalcitonin.

Moreover, the low ability of such biomarkers to accurately predict co-infection was confirmed through the ROC curve analysis, obtaining poor AUC results (0.56 for PCT and 0.54 for CRP). Additionally, a non-linear model performed using the CHAID analysis showed that neither PCT nor CRP levels were related to co-infection, which reinforced our findings.

A recent multicenter cohort study conducted in United Kingdom including 1040 hospitalized adults with SARS-CoV-2 infection [25], observed that PCT was not a useful biomarker or which provided an added clinical value to predict bacterial co-infection, reporting an AUROC 0.56, which coincide with the findings we reported in our cohort. The investigators found higher incidence of bacterial co-infection compared with our study, maybe due to the fact that one of the inclusion criteria was the requirement of blood and respiratory cultures at hospital admission. Additionally, two third of patients were diagnosed of co-infection with respiratory cultures, but only one third of the cohort needed mechanical ventilation, which implied that most of respiratory cultures results were taken from the upper respiratory tract trough sputum, hence, with more probability of overdiagnosis of bacterial infection, especially when the quality of sputum is poor. They recognized that rates of recorded microbiological investigation were low and culture positivity was high, whereby there may be a bias for preferential recording of positive microbiology results in their database. Conversely, almost 90% of patients with bacterial co-infection in our cohort of critically ill patients were mechanically ventilated, in whom the respiratory cultures were taken from the lower respiratory tract by tracheal aspirate or bronchoalveolar lavage. Moreover, the authors could not provide NPV to avoid misleading conclusions due to its highly selected cohort. Our study adds more valuable information in reporting a high NPV with a PCT<0.3ng/mL threshold as it could be used for antibiotic stewardship decisions and avoiding unnecessary empirical antibiotics in the care of critically ill patients.

PCT production is stimulated by bacterial endotoxin and proinflammatory cytokines (IL-6, IL-1β, and TNF-α) but inhibited by interferon-gamma cytokine produced during viral infections. Given that PCT has relentlessly demonstrated its ability to discriminate between viral and bacterial pneumonia [27,28], it was faithfully believed that it could be helpful to distinguish the presence of bacterial co-infection in COVID-19 pneumonia. Nonetheless, several observational data have addressed this topic, with unexpected results as our findings. Some small studies [29,30] observed that PCT levels were not useful to predict bacterial co-infection. In a larger retrospective study [31] including 2443 non-critical patients, PCT cut-offs (0.25 or 0.50 ng/ml) did not reliable identify co-infection. Also, Dolci et al. [32] investigated PCT and CRP levels in a small cohort of 83 hospitalized COVID-19 patients. They found that both biomarkers had AUCs < 76 with poor PPV to predict bacterial co-infection. Interestingly, the authors observed that the threshold of PCT <0.25 ng/ml held a high NPV (91.7%) to exclude co-infection. Similarly, our study found a helpful cut-off point of PCT <0.3 ng/ml to rule out bacterial co-infection with an NPV of 91.1%. These findings are of particular interest in critical care practice as values of PCT <0.3ng/ml might be useful to avoid unnecessary empirical antibiotic treatment and, thereby, make better use of antibiotics consumption. During the COVID-19 pandemic, there has been a widespread use of antimicrobials in spite of the low incidence of bacterial co-infection although its consequences over the antibiotic resistances and the health-care costs are still uncertain. Our data findings indicate that early hospitalization, bacterial co-infection in severe COVID-19 is uncommon and support the recommendations that empirical antibiotics should not be started routinely at admission without clinical suspicion of bacterial co-infection. Thus, baseline values of PCT <0.3 ng/ml might be a helpful for antibiotic stewardship programs, avoiding the antibiotic overprescribing and reducing the inappropriate use of such treatments.

Case in point, CRP is synthesized in response to cytokines IL-6 and IL-1 as an early but unspecific acute-phase inflammatory biomarker. However, it is well known that it has low specificity to predict bacterial etiology in respiratory infections [27]. This is also in alignment with our findings. CRP levels were not an accurate reliable tool to predict bacterial co-infection. To date, there is no data regarding the power of CRP by itself to predict bacterial co-infection in the COVID-19 scenario.

The predictive mortality value of biomarkers has also been investigated during the pandemic. Our data showed that PCT and CRP levels at admission were higher among non-survivors. However, only values of PCT >0.5ng/ml were independently associated with higher mortality, whereas CRP levels were not a prognostic factor. Our study found that most of the patients had normal PCT levels at ICU admission, which is consistent with past reported measures by other authors [29,33]. However, many studies coincided that high PCT levels upon admission are associated with worse clinical outcomes. The meta-analysis conducted by Lippi et al. showed that increased PCT values were associated with a

higher risk of severe SARS-CoV-2 infection (OR, 4.76; 95% CI, 2.74–8.29). Su et al. [34], in a retrospective study of 651 severe COVID-19 patients, found that PCT >0.1ng/mL on admission was independently associated with increased in-hospital death (OR 6.35, 95% CI 1.39-28.88, p = 0.017). Also, two recent metanalyses concluded that elevated PCT levels were significantly associated with increased mortality (24,30), suggesting that the best threshold may be PCT >0.5ng/ml. Likewise, all these findings are in line with our results, in which PCT ≥0.50 ng/mL was independently associated with ICU mortality (OR 1.5, 95% CI 1.21-1.88; p <0.001). Conversely, only a few smaller studies have not found an association between PCT and mortality [29,36,37]. Despite our findings suggested that PCT had a low discriminatory performance to distinguish bacterial co-infection, it might still aid in predicting poor prognosis among COVID-19 patients admitted to the ICU. This could be explained by the hyperinflammatory state induced by the SARS-CoV-2 infection with the consequent and extensive release of cytokines [38], resulting in greater production of PCT as a marker of a more severe viral infection, regardless of the presence of bacterial co-infection. While CRP values seemed to be associated with higher disease severity [39,40] and the development of acute respiratory distress syndrome [41], several studies have reported that CRP levels were not independently associated with death [35,37,41], in accordance with our research.

Although PCT thresholds could be helpful to exclude bacterial co-infection regardless of its ability to predict prognosis, further research exploring the predictive ability of bacterial co-infection with combination of CRP and PCT may provide additional results to guide clinical decisions when there is clinical suspicion of bacterial co-infection in COVID-19 patients. There is recent data that suggests that the combination of PCT and CRP levels showed greater accuracy to predict bacterial co-infection in children with influenza H1N1 [42]. Furthermore, not only CRP and PCT levels need to be investigated in additional studies but also some new biomarkers such as inflammatory mediators in the bronchoalveolar lavage fluid, the detection of bacterial genetic code by molecular amplification techniques by polymerase chain reaction and omics which could provide promising results and useful information for clinical decision making in the diagnoses of bacterial co-infection among patients with suspected sepsis [43].

To the best of our knowledge, this is one of the largest studies evaluating the diagnostic accuracy of PCT and CRP to predict bacterial co-infection and its prognostic value among ICU patients with COVID-19 pneumonia. The main strengths of this analysis were the inclusion of a sizeable homogeneous cohort of critical COVID-19, the multicentric design across ten countries in Latin America and Europe, and the use of distinct statistical methods to evaluate and confirm our primary outcome. However, we acknowledge some limitations present in the analysis. First, the retrospective design nature may have introduced a selection bias that frequently arises in observational studies. Nevertheless, the study was conducted in a homogeneous cohort of critically ill patients, and potential confounding factors have been considered. Second, the exclusion criteria were based on PCT and CRP's missing data, which could result in higher inclusion of patients with bacterial co-infection. Missing data may introduce bias, primarily if such data are not appropriately handled. However, considering the pandemic context and the large dataset of the study, we could assume that the underlying mechanism might be due to missing data entirely at random. Therefore, in such a case, the results can be said to carry less bias and only affected by a reduced statistical power.

Even so, after the exclusion criteria, the sample size was considerably large and the final dataset for the analysis had a negligible rate of missing values (less than 5%) in most variables. Third, antibiotic administration before the ICU admission was not collected, which could have influenced a misclassification of some patients with negative respiratory cultures, hence the classification in the non-co-infection group. However, the observed bacterial co-infection incidence was similar to that reported in previous data. Several international guidelines during the pandemic, recommended to initiate empirical antibiotics at admission for severe COVID-19, which led to most patients receiving empirical antimicrobial treatment at hospital admission. In this context, the true incidence of co-infection could be difficult to know. Nevertheless, our study provides real data of clinical practices from an international cohort of critically ill patients and, therefore, the observed incidence could be considered very close to the real incidence of co-infection, globally. Additionally, prior antibiotics could influence the levels of biomarkers. Nonetheless, co-infected patients only took one day between the hospital arrival and ICU admission, therefore, the levels of biomarkers were taken early in the acute phase of the illness, which makes the results as valid due to a proper sample timing.

Fourth, biomarker levels could be influenced by immunomodulatory therapies such as tocilizumab and corticosteroids. Nevertheless, it has been observed that the decreased of CRP after tocilizumab and corticosteroid treatment is progressive and this reduction appears to be significant after the 72 hours of treatment initiation, whereas the effects on PCT might be less pronounced [44–46]. In our study, biomarker levels were taken within the first 48 hours of hospital admission, hence, the influence of these treatments on biomarkers is low, yielding a reliable analysis. Fifth, attrition bias may occur when large number of participants drop out from a study, which might have an influence on the results. Most of excluded patients, dropped out due to missing data on biomarker levels, our variable of interest. Nevertheless, excluded patients had similar characteristics in terms of demographics, illness severity, time course of disease and outcomes, without relevant clinical differences that could influence the values of baseline biomarkers. Moreover, the incidence of bacterial co-infection in the excluded group was low (3.8%), hence, the exclusion of such subjects probably would not affect the results and the diagnostic performance of biomarkers to predict bacterial co-infection. Sixth, we recognize moderate imbalanced data on the incidence of bacterial co-infection leading to class imbalance when performing logistic regression analysis, as predictive models tend to be more biased towards majority classes. Notwithstanding, recent research suggests that logistic regression model in our analysis is reliable as imbalance ratio effect is limited with larger sample sizes, whereby the estimates get closer to the true value when the sample size increases [47,48].

The latter suggests, that procalcitonin and C-reactive protein did not successfully identify bacterial co-infection among ICU patients with COVID-19 pneumonia. However, a threshold of procalcitonin <0.3 ng/ml may be helpful to rule out bacterial co-infection. Therefore, it allows clinicians to carry out the proper use of antibiotics and limit its overuse. Finally, elevated procalcitonin concentration on admission may be a helpful biomarker to predict prognosis. Further research should be conducted to verify our findings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.06.024.

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