Procalcitonin may help in diagnosing bacterial infections in COVID-19 patients during high-dose steroid therapy

Ayse Batirel[1], Nurullah Eser[1], Ezgi Korlu[1], Mehmet Engin Tezcan[2]
[1]Kartal Lutfi Kirdar City Hospital, Department of Infectious Diseases, Istanbul, Turkey
[2]Kartal Lutfi Kirdar City Hospital, Department of Rheumatology, Istanbul, Turkey

Key words: *Coronavirus disease-19, procalcitonin, bacterial infection*

Dear Editor,

SARS-CoV-2 infection (COVID-19) is a multi-system disease that mainly affects the lung from mild pneumonia to acute respiratory distress syndrome (1). It has recently been shown that high-dose steroid therapy can reduce mortality rate in hypoxic COVID-19 patients (2). In these cases, the diagnosis and the monitoring of a bacterial infection may be a challenging issue (3). Since procalcitonin (PCT) is a well-established marker for systemic bacterial infection, it can be used during high-dose steroid therapy to distinguish clinical and laboratory alterations due to the uncontrolled inflammation caused by COVID-19 from bacterial superinfection (4). In our hospital, the COVID-19 patients receive high dose steroid treatment at a dosage of 6 mg once a day from the onset of hypoxia. However, the utility of PCT as a marker of infection, during COVID-19 infection and high-dose steroid therapy is potentially reduced since severe COVID-19 diseases may increase PCT levels (5) and steroid therapy may unexpectedly reduce PCT level (6), particularly by suppressing inflammation associated with COVID-19, even if bacterial superinfection occurs during the treatment. We report here about the validity of the use of PCT to diagnose bacterial superinfection during high-dose steroid therapy. A second aim of this report is to identify a PCT decision limit to more successfully diagnose the presence of a bacterial infection thus reducing antibiotic misuse.

267 consecutive hospitalized and hypoxic COVID-19 patients who received high-dose steroid therapy (Dexamethasone 6 mg/day equivalent dose steroid) have been enrolled for the study; their medical records have been examined retrospectively. The diagnosis of COVID-19 was made on the basis of a positive SARS-CoV2 nasopharyngeal swab or if the patients fulfilled three clinical criteria: high temperature (>37.5 C°), respiratory symptoms, showing compatible chest imaging findings (7) and decreased lymphocyte count (<1000 x10^9/L) while the white blood cell count was normal or decreased. High dose steroid treatment was initiated at the onset of hypoxia and the patients received the steroid treatment according to clinical evaluation. The presence of a bacterial infection was diagnosed by an infectious disease specialist and was based on clinical, laboratory and imaging screening methods (tomography, ultrasound, magnetic resonance) as needed. All laboratory variables were obtained from hospital medical database. Demographic and disease related features of the COVID-19 patients in our cohort are shown in Table 1. The decision limits of the laboratory tests shown in Table 1 are indicated according to their relationships with severe disease (8). PCT levels were measured every other day during high-dose steroid therapy and also after the treatmentif there were clinical signs of a bacterial infection. PCT concentrations were measured in serum samples by an electrochemiluminometric immuno assay within 24 hours from the blood collection using the Roche Modular E-170 analyser. The analytical sensitivity of the method is ≤0.02 ng/mL; the functional sensitivity is 0.06 ng/mL. PCT concentrations are presented in Table 2. For patients without bacterial infection, the highest value during the steroid treatment has been considered; for patients diagnosed with bacterial infection the PCT value measured just before the diagnosis has been used. Since PCT values are not normally distributed, we applied the Mann-Whitney U test and Chi-square tests where appropriate. We also made the ROC curve to determine the cut-off PCT value for infection in patients. Continuous values are shown with median (IQR). $p<0.05$ was considered significant. This study was approved by both the Local Research Ethics Committee prior to data collection and carried out in compliance with the Helsinki Declaration as amended in 2013.

17 out of 267 COVID-19 patients on high dose steroid treatment (6.4%) was diagnosed with bacterial infection (Table 2); the different sites of the infection are listed in Table 2 together with the respective PCT serum concentrations PCT levels

Corresponding Author: Mehmet Engin Tezcan, MD. (Orcid no: 0000-0002-1753-4936), Trainig and Research Hospital, Department of Rheumatology, Kartal, 34680, Istanbul-TURKEY, Tel +902164583000, E-mail engintez@yahoo.com

Ricevuto: 18.02.2021 Revisionato: 17.03.2021 Accettato: 18.03.2021

Pubblicato on-line: 16.04.2021 DOI: 10.19186/BC_2021.020

Table 1
Demographic and disease related features of the COVID-19 patients

Age, years, median (IQR)	62.0 (52.0-72.0)
Gender (M/F)	159/108
Positive nasopharyngeal swab, n (%)	236 (88.4)
Length of steroid treatment, days (IQR)	6.0 (5.0-8.0)
Time to onset of symptoms to oxygen supplementation, days, median (IQR)	3.0 (2.0-6.0)
Time to hospitalization to initiation of steroid therapy, days, median (IQR)	1.0 (1.0-1.5)
Disease severity (NEWS-2 score)*, median (IQR)	3.0 (1.0-5.0)
Low, n (%)	165 (62.1)
Moderate, n (%)	56 (21.0)
High, n (%)	45 (16.9)
Symptoms n (%)	
Cough	174 (65.2)
Shortness of breath	139 (52.1)
Fever	100 (37.5)
Musculoskeletal	61 (22.8)
Headache	19 (7.1)
Sore throat	10 (3.7)
Loss of taste or smell	7 (2.6)
Malaise	115 (43.1)
Diarrhoea	19 (7.1)
Nausea/vomiting	37 (13.9)
Loss of appetite	22 (8.2)
Co-morbidities	
Charlson comorbidity index score, median (IQR)	3.0 (1.0-5.0)
Diabetes mellitus, n (%)	82 (30.7)
Hypertension, n (%)	120 (44.9)
Coronary arterial disease, n (%)	46 (17.2)
COPD, n (%)	12 (4.5)
Asthma, n (%)	19 (7.1)
Malignancy, n (%)	24 (9.0)
Chronic renal disease, n (%)	16 (6.0)
Rheumatic diseases, n (%)	5 (1.9)
Clinical Chemistry**	
Transaminases (>35 IU/L), n (%)	107 (40.1)
Creatinine (>1.2 mg/dL), n (%)	69 (25.8)
LDH (>240 U/L), n (%)	173 (64.8)
D-dimer (≥1000 ng/mL), n (%)	112 (41.9)
Lymphocyte (≤1x109/L), n (%)	133 (49.8)
Ferritin (≥300 mg/mL), n (%)	151 (56.6)
CRP(>10 mg/dl), n (%)	123 (82.0)
Outcome	
Deceased, n (%)	18 (6.7)
Requirement of ICU, n (%)	21 (7.9)
Requirement of MV, n (%)	16 (6.0)
Length of hospitalization, days (IQR)	7.0 (5.0-10.0)
Infection, n (%)	17(6.4)

IQR, Interquartile Range; M, Male; F, Female; COPD, Chronic obstructive pulmonary disease; ICU, Intensive care unit; MV, Mechanical ventilation; NEWS-2, National Early Warning Score-2; CRP, C reactive protein; LDH: Lactate dehydrogenise.
**At the onset of hypoxia*
***The values in brackets are those related to negative outcomes (8).*

Table 2
Procalcitonin levels of the COVID-19 patients with different bacterial infection types

	Procalcitonin (ng/mL)
Patient without infection (n=250)	0.09 (0.06-1.0)
Patient with infection (n=17)	2.4 (0.6-14.5)
Pneumonia (n=10)	2.8 (0.6-7.5)
Blood stream infection (n=3)	0.8 (0.6-1.8)
Urinary tract infection (n=2)	8.8 (0.7-17.0)
Soft tissue infection (n=2)	27.8 (25.7-30.0)

Data are presented as medians and InterQuartile Range.

were significantly higher in patients with infection than in patients without infection (p<0.001); all patients with infection had PCT levels higher than the usually adopted decision limit (0.15 ng/mL), as expected (9).11/17 (64.7%) of the patients were diagnosed with infection while receiving steroid therapy; the other 6 patients were diagnosed with infection after cessation of steroid therapy. The median time between the onset of steroid treatment and infection diagnosis was 7.0 (IQR 6.0-10.0) days. In addition, the median time between hospitalization and initiation of steroid therapy was 1.0 (IQR 1.0-1.5) days. 55 of 250 (22.0%) of the patients without infection had PCT levels higher than 0.15 ng/mL. According with the ROC curve, PCT higher than 0.25 ng/mL is the best cut off value for diagnosing infection in our cohort (sensitivity 94.1%, specificity 84.4 %) with a likelihood ratio of 6.03 [Confidence interval at 95% (CI 95%) 4.2.-8.4] and a negative likelihood ratio of 0.07 (CI 95% 0.01-0.47). A concentration of 0.15 ng/mL shows a similar sensitivity (94.1%) with slightly lower specificity (78.0%). Changing the decision limit of PCT from 0.15 ng/ml to 0.25 ng/ml can prevent 16 (6.4%) patients from misusing antibiotics due to increased PCT levels with the same success rate for diagnosing bacterial infections. The odds ratio for a bacterial infection diagnosis in a COVID-19 patient receiving high-dose steroids with PCT greater than 0.25 ng mL was 86.5 (CI 95% 11.1-671.7, p <0.001). This large CI interval may be related to the limited sample size of the study and to the presence of outliers.

In this study where the usefulness of PCT as a bacterial infection marker in COVID-19 patients receiving high-dose steroids has been examined, more than 20% of patients without infection have PCT values above the usual cut-off (0.15 ng/mL). While PCT can still be used to diagnose bacterial infections with high sensitivity in these patients, at this value, the risk of antibiotic misuse is higher compared to setting the cut-off value to 0.25 ng/mL. The hypothesis that high dose steroidt herapy could inappropriately lower PCT levels in the course of a bacterial infection in COVID-19 patients was not proved in this study. As a conclusion, the usual decision level of PCT (0.15 ng/mL) can be used in daily hospital practice to diagnose a bacterial infection while treating COVID-19 patients with high dose steroid treatment, with a slight increase of the risk of antibiotic misuse. A decision limit of 0.25 ng/mL can be used to alert clinicians of a possible bacterial infection with acceptable sensitivity and specificity, reducing the risk of antibiotic misuse, as demonstrated in a recent study (10).

CONFLICT OF INTEREST

None.

REFERENCES

1. Rothan HA and Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109:102433.
2. Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19 - Preliminary Report. N Engl J Med 2021;384:693-704.
3. Noone T. An overview of steroid use and its potential side-effects. Nurs Times 2006;102:24-7.
4. Hamade B,Huang DT. Procalcitonin: where are we now? Crit Care Clin 2020;36:23-40.
5. Hu R, Han C, Pei S, et al. Procalcitonin levels in COVID-19 patients. Int J Antimicrob Agents 2020;56:106051.
6. Tamaki K, Kogata Y, Sugiyama D, et al. Diagnostic accuracy of serum procalcitonin concentrations for detecting systemic bacterial infection in patients with systemic autoimmune diseases. J Rheumatol 2008;35:114-9.
7. Yang Q, Liu Q, Xu H, et al. Imaging of coronavirus disease 2019: A Chinese expert consensus statement. Eur J Radiol 2020;127:109008.
8. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
9. Meisner M. Update on procalcitonin measurements. Ann Lab Med 2014;34:263-73.
10. Peters C, Williams K, Un EA, et al. Use of procalcitonin for antibiotic stewardship in patients with COVID-19: A quality improvement project in a district general hospital. Clin Med (Lond) 2021;21:e71-e76.