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CE - LETTER TO THE EDITOR

Procalcitonin for the differential diagnosis of COVID-19 in the emergency department. Prospective monocentric study

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Dear Editor,

In patients presenting to emergency departments (EDs) with fever or respiratory complains, ruling out Coronavirus disease 2019 (COVID-19) is a new major challenge. Reverse transcriptase-polymerase chain reaction (RT-PCR) of respiratory specimens is the standard of care for COVID-19 diagnosis although it has some limitations such as a turnaround time of hours and a non-negligible false negative rate [1]. Those limitations have pushed to test the contribution that laboratory markers could have in COVID-19 differential diagnosis. In EDs, laboratory test panels containing preselected tests are commonly used to speed up and simplify physician's work. During COVID-19 outbreak, several EDs introduced laboratory test panels including procalcitonin (PCT) for patients with suspected COVID-19 (COVID-19 panel). PCT is a laboratory marker whose values are not substantially modified in viral infections and a PCT cut-off 0.5 ng/mL has been previously studied in differential diagnosis between viral and bacterial infections [2]. The aim of this prospective, observational, single center before and after study is to evaluate if a PCT ≥ 0.5 ng/mL could help for the differential diagnosis of COVID-19 from other causes of fever and respiratory symptoms and in particular non-COVID-19 pneumonia. Furthermore, we evaluate whether the introduction of PCT in the COVID-19 panel was associated with differences outcomes.

Consecutive patients presenting to the ED of an Italian tertiary-care university hospital were enrolled from the 7th to the 27th of April 2020. Inclusion criteria were: (a) age ≥ 18 years; (b) referred fever or body temperature > 37.5 °C or respiratory symptoms or signs (dyspnea, cough, pharyngitis, oxygen saturation ≤ 94% in room air, respiratory rate ≥ 20 per minute) (c) request by the treating physician of the COVID-19 panel; exclusion criteria were: (a) presentation to ED with a known diagnosis of COVID-19; (b) presentation on the 17th of April 2020, the day of intervention, when PCT was included in COVID-19 panel; (c) loss of the patient at follow-up. Informed consent was obtained from the patients included in the study.

During the pre-intervention period (from the 7th to the 16th of April 2020), the COVID-19 panel included: complete blood count, fibrinogen, prothrombin time/international normalized ratio, activated partial thromboplastin time, glucose, creatinine, sodium, potassium, ALT, total bilirubin, LDH, C reactive protein, interleukin-6. During the pre-intervention period, PCT could be requested by treating physician without restrictions adding it to the COVID-19 panel. Starting from the 17th of April 2020, PCT was included in the COVID-19 panel and intervention period lasted from 18 to 27th of April 2020. PCT was measured using an automated Enzyme-Linked Fluorescent Assay (ELFA): VIDAS® B.R.A.H.M.S PCT™ (Vidas, BioMerieux) and the PCT cut-off chosen was 0.5 ng/mL as recommended and already in use in our ED [3, 4]. Final case adjudication was performed by two expert physicians (one Internal Medicine specialist with 20 years of medical experience and one Emergency Medicine Specialist with 13 years of medical experience) who independently assessed each patient. Patients with a positive rRT-PCR test in any

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naso-pharingeal swab and/or bronchoalveolar lavage within 5 days from ED index visit were diagnosed with COVID-19. In the other cases, the diagnosis was established considering all hospital and 30-day follow-up data. In patients with COVID-19 diagnosis, the experts also established if pneumonia was present or not. When COVID-19 was excluded, a preselected standardized alternative diagnosis was established in particular non-COVID-19 infection and non-COVID-19 pneumonia. In case of discordant adjudication, a third expert specialized in Internal Medicine and Pulmonary Medicine with 35 years of medical experience adjudicated the final diagnosis. Furthermore, we evaluate if the introduction of PCT in the COVID-19 panel caused a change between the pre-intervention and intervention period regarding 30-day hospital admission and death.

The study included 444 patients, 231 (52%) in the pre-intervention period and 213 (48%) in the intervention period. There was no significant difference in medical history, clinical features, and laboratory results for patients in the pre-intervention and intervention period. Out of 444 patients, 98 (22%) were finally diagnosed with COVID-19, of whom 89 (20%) with COVID-19 pneumonia. Only one patient received a final diagnosis of COVID-19 pneumonia with a proved bacterial co-infection.

In the 213 patients of the intervention period, the result of PCT was ≥ 0.5 ng/mL in 53 (24.9%) cases, including 9 (26.5%) of the 34 COVID-19 and 44 (24.6%) of 179 patients with an alternative diagnosis ($p = 0.815$). PCT was ≥ 0.5 ng/mL in 28 (38.4%) of 73 patients with a final diagnosis of non-COVID-19 infection ($p = 0.229$ vs. COVID-19). Median PCT in COVID-19 patients was 0.2 ng/mL (iqr = 0.42), whereas in the patients with alternative diagnosis was 0.12 ng/mL (iqr = 0.40), ($p = 0.575$) and in patients with non-COVID-19 infection was 0.25 ng/mL (iqr = 0.88), ($p = 0.589$ vs. COVID-19). Considering the subgroup of 60 patients with a final diagnosis of pneumonia, 32 (53.3%) were COVID-19 pneumonia whereas 28 (46.7%) were non-COVID-19 pneumonia. Among 32 patients with COVID-19 pneumonia, 9 (28.1%) had a PCT ≥ 0.5 ng/mL while among 28 patients with non-COVID-19 pneumonia, 12 (42.9%) had a PCT ≥ 0.5 ng/mL (p = 0.233). Median PCT in the COVID-19 pneumonia was 0.24 ng/mL (iqr = 0.47) whereas in non-COVID-19 pneumonia was 0.21 ng/mL (iqr = 0.83) ($p = 0.638$). Table 1 reports the diagnostic performance of PCT ≥ 0.5 ng/mL for non-COVID-19 pneumonia vs. COVID-19 pneumonia.

In the pre-intervention period, when PCT was not included in the COVID-19 panel, PCT was requested by the treating physician in only 20 patients. The PCT requested in ED during the intervention period increased of 965% (+ 193 tests). The PCT cost was 740 euros (equivalent to 908 United States dollar, US$) in the pre-intervention period and 7881 euros (equivalent to 9665 US$) in the intervention period (+ 7141 euros or 8758 US$ in 10 days). Including PCT in the COVID-19 panel had no significant impact in the prognostic outcomes (Table 2).

Table 1 Diagnostic performance of PCT ≥ 0.5 ng/mL for non-COVID-19 pneumonia vs COVID-19 pneumonia

TP	12
FP	9
TN	23
FN	16
Overall accuracy	58.3% (44.9–70.9%)
Sen % (95% CI)	42.9% (24.5–62.8%)
Spec % (95% CI)	71.9% (53.3–86.3%)
PPV % (95% CI)	57.2% (39.9–72.9%)
NPV % (95% CI)	60% (49.4–67.9%)
+ LR (95% CI)	1.52 (0.76–3.07)
− LR (95% CI)	0.8 (0.54–1.17)

TP true positive, *FP* false positive, *TN* true negative, *FN* false negative, *Sen* sensitivity, *Spec* specificity, *NPV* negative predictive value, *PPV* positive predictive value, *+LR* positive likelihood ratio, *− LR* negative likelihood ratio, *95% CI* 95% confidence interval

Our study showed that PCT is not useful for differential diagnosis of COVID-19 in ED in patients presenting with fever or respiratory symptoms. Furthermore, the inclusion of PCT in the COVID-19 panel did not change prognosis, while costs increased more than 10 times. PCT ≥ 0.5 ng/mL showed to be a marker for the diagnosis of bacterial infection [4]. Our study was performed in April 2020 in Italy, when the flu season was over, and without COVID-19 outbreak, we would expect that most of infections and in particular pneumonia would be caused by bacteria [5]. However, a PCT ≥ 0.5 ng/mL was not helpful to distinguish COVID-19 from other infections. Considering the subgroup of patients with pneumonia, in which the differential diagnosis is more important, PCT ≥ 0.5 ng/mL showed a low sensitivity (43%) and specificity (72%) for non-COVID-19 pneumonia. This study has limitations: it does not include randomization and it was carried out in a single University Hospital.

In conclusion, PCT showed to be not useful to distinguish COVID-19 vs alternative cause of fever and respiratory symptoms and in particular, it was not accurate to identify non-COVID-19 pneumonia. Furthermore, including PCT in the COVID-19 laboratory panel increased costs without modify patients' prognosis.

When deciding whether to request PCT in ED, we favor a case-by-case decision in presence of sepsis or in presence of COVID-19 with suspected bacterial superinfections vs the inclusion in a laboratory test panel.

Table 2 Outcomes within 30 days between pre-intervention and intervention period

	Total ($n=444$)	Pre-intervention period ($n=231$)	Intervention period ($n=213$)	p value
Admissions to hospital	317 (71.4%)	173 (74.9%)	144 (67.6%)	0.09
ICU admissions	20 (4.5%)	8 (3.5%)	12 (5.6%)	0.271
Deaths	53 (11.9%)	31 (13.4%)	22 (10.3%)	0.277

Values are reported as absolute number and percent value within column in brackets for categorical data

ICU intensive care unit

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Compliance with ethical standards

Conflict of interest None of the authors and of the study investigators report conflict of interest except for Prof. Rossolini that received honoraria by Thermofisher for participation in advisory boards on PCT diagnostic use in bacterial infections.

Statement of human and animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent All participants provided informed consent prior to their participation.

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