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Original

Does procalcitonin play a role as a predictor of in-hospital mortality among COVID-19 patients admitted to intensive care unit?

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Abstract

Introduction: Inflammatory response plays a key role in coronavirus disease 2019 (COVID-19) as it has been shown that the resulting cytokine storm increases its severity.

Objectives: To investigate the role of procalcitonin (PCT) as a predictor of in-hospital mortality in patients with severe to critical COVID-19.

Patients and Methods: In a retrospective cohort study, 150 patients with severe to critical COVID-19 consecutively admitted to the intensive care unit (ICU) were investigated. Patients' demographics, clinical and laboratory findings, and PCT level were collected upon their admission to the hospital and from the disease outcome data.

Results: Of the 150 patients who entered the study, 77 were discharged alive from the hospital. The mean age of the patients was 60.9 ±16.3 years and 51.3% of them were male. The mean PCT level was significantly higher in the deceased patients than in survivors (2.4 ± 3.4 versus 0.7±1.3, $P<0.005$). The logistic regression analysis indicated that PCT, creatinine and urea levels were independently associated with in-hospital mortality.

Conclusion: Serum PCT levels are associated with in-hospital mortality in COVID-19 patients admitted to ICU and could be used as a simple tool to predict adverse outcomes and expedite timely and appropriate interventions.

Keywords: COVID-19, Procalcitonin, Outcome, Mortality, Severity

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread quickly in its recent outbreak resulting, by early March, 2021, in almost 120 million confirmed cases and more than 2.6 million deaths (John Hopkins University) (1), the clinical spectrum of SARS-CoV-2 infection is wide, encompassing asymptomatic or mild infections and severe illness with high mortality rates, mainly caused by respiratory failure (2). Several prognostic factors have been explored in COVID-19 patients. However, there is still no reliable index with which to predict the outcome of the disease and thereby help detect the potentially high-risk cases early. Procalcitonin (PCT) is a recognized, specific marker of bacterial infection in patients suspected of sepsis (3). It is also a good marker for the start of antibiotic treatment in patients hospitalized in emergency rooms for respiratory infections (4,5). The level of PCT increases as the result of systemic inflammations, especially during bacterial infections (6,7). Moreover, it seems that PCT level is an important marker for severe disease and adverse outcome in patients with SARS-CoV-2 infection (8).

Objectives

The purpose of this study was to investigate the role of PCT as a predictor of adverse outcome in COVID-19 patients admitted to the intensive care unit (ICU).

Patients and Methods

Study design

In this retrospective cohort study, 150 COVID-19 patients admitted to the ICU of the Imam Khomeini hospital, Iran during the period march-September 2020 were investigated. The patients were diagnosed with SARS-CoV-2 infection based on the results of a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on nasopharyngeal swab and chest CT. Patient demographic information, comorbidities, lab test results, including PCT value (within 24h of ICU admission), length of in-hospital stay, vital signs, need for ventilatory

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Implication for health policy/practice/research/ medical education

High serum procalcitonin level is significantly associated with adverse outcome in COVID-19 patients and can be used as a predictor of mortality.

support, use of antibiotics, and disease outcomes were all collected from electronic medical records.

Statistical analysis

For statistical analyses, SPSS version 19 was employed. The significance level for all of the tests was set at 0.05 and all of the results were reported in the form of the mean values ± standard deviation. To compare different variables, the statistical tests of Mann-Whitney U and chi-square were used. Additionally, *t* test and regression tests were conducted too. The prognostic value of PCT was assessed by receiver-operating characteristic analysis. Moreover, Youden index was calculated to obtain the optimal threshold value. In order to determine those factors that predict in-hospital mortality, a logistic regression analysis by was conducted.

Results

Among the 150 patients suffering from severe COVID-19 who entered the study, 77 cases were discharged alive from the hospital and 73 cases died. The mean age was 60.9 ± 16.3 (age range 21-93 years), and 51.3% were male. 68% of the patients were intubated, 57.3% suffered from severe hemodynamic disorder, and 42% had fever. The most prevalent background disease was diabetes (18%). The mean length of hospital stay was 18 ± 11.8 days. Among the deceased patients, death occurred on average 15.5 ± 10.6 days after ICU admission. Around 20.5% of the patients who died had diabetes and 10.9% of them suffered from chronic renal failure. The study population was divided into 2 groups based on the disease outcome (survivors versus non-survivors). Patient demographics, comorbidities and length of hospital stay (Table 1) and laboratory results (Table 2) are presented separately for each group.

The area under the ROC curve for PCT was 0.727 (Figure 1, Table 3). Based on this figure, the optimum cut-off point for PCT as a predictor of in-hospital death was determined to be 0.12, with a sensitivity of 90% and a specificity of 68%.

The PCT level in the deceased patients was significantly higher than that of the survivors (2.43±3.40 versus 0.73±1.28). In order to determine the relationship between serum PCT and in-hospital death, binary logistic regression was used, the results of which are summarized in Table 4. The logistic regression analysis indicated that PCT, creatinine and urea levels were independently associated with in-hospital mortality. More specifically, an increase of 1 unit in PCT level led to an increase of 0.66% in the mortality risk of COVID-19 patients (OR= 0.668; 95% CI: 0.518-0.862). Additionally, an increase of one unit in creatinine and urea level led to an increase of respectively 1.25% and 0.98% in the mortality risk of COVID-19 patients.

Discussion

The aim of this study was to explore the role of PCT as a predictor of adverse outcome in a cohort of patients affected by severe to critical COVID-19. For this purpose, 150 COVID-19 patients hospitalized in ICU were investigated. The results showed that serum PCT level in the deceased patients was significantly higher than that of the survivors. The logistic regression model confirmed the positive correlation between PCT and mortality, meaning that as serum PCT level increases, mortality also increases.

Table 1. Patient demographics, comorbidities, and length of hospital stay in separate groups

Variables	All patients (n = 150)	Survivors (n = 77)	Non-survivors (n = 73)
Age (y)	60.92 ± 16.33	55.47 ± 16.35	66.51 ± 14.40
Gender			
Male	77	44	33
Female	73	32	41
Hospitalization time (9)	18.01 ± 11.87	18.99 ± 11.26	17.03 ± 12.57
Underlying disease, n (%)			
Hypertension	16(10.6)	10 (12.9)	6(8.2)
Chronic kidney disease	13(8.6)	5 (6.4)	8(10.9)
Diabetes mellitus	27(18)	12(15.5)	15(20.5)
Coronary artery disease	10(6.6)	7(9)	3(4.1)
Cancer	3(2)	1(0.6)	2(1.2)
Endotracheal intubation, n (%)	105 (70)	32 (41.6)	73 (100)
Hemodynamic instability, n (%)	86 (57.3)	26 (34.2)	60 (81.1)
Fever, n (%)	63 (68)	21(16)	42 (81.1)

Table 2. Laboratory findings of patients in separate groups

Variables	All patients (n = 150)	Survivors (n = 77)	Non-survivors (n = 73)	*P* value
White blood cells (10^9/L)	8314.57 ± 3221.10	7404.73 ± 4371.268	8055.21 ± 4018.957	0.45
Procalcitonin (ng/mL)	1.57 ± 2.69	0.73 ± 1.28	2.43 ± 3.40	0.001*
Platelets (10^9/L)	149040.28 ± 121002.44	161199.45 ± 130695.27	136552.49 ± 109652.43	0.27
NLR	8.51± 9.10	7.08 ± 9.53	10.02± 8.43	0.048
Hb (g/dL)	12.99 ± 2.49	13.11 ± 2.37	12.86 ± 2.61	0.56
Urea (mg/dL)	53.17 ± 40.29	42.11 ± 28.60	64.54 ± 47.06	0.000*
Cr (mg/dL)	1.44 ± 1.27	1.32 ± 1.43	1.56 ± 1.08	0.002*
Mg (mg/dL)	2.07 ± 0.57	2.04 ± 0.55	2.09 ± 0.59	0.26
Na (mg/dL)	138.87 ± 6.31	138.97 ± 5.79	138.77 ± 6.83	0.84
K (mg/dL)	4.28 ± 0.90	4.27 ± 1.10	4.29 ± 0.65	0.13
Ca (mg/dL)	8.25 ± 0.78	8.34 ± 0.83	8.16 ± 0.72	0.16
P (mg/dL)	3.65 ± 1.35	3.49 ± 0.80	3.81 ± 1.74	0.77

Abbreviations: NLR, Neutrophil to lymphocyte ratio; Hb, hemoglobin; Cr, creatinine; Mg, magnesium; Na, sodium; K, potassium; Ca, calcium; P, phosphorus.
Notes: * $P < 0.05$ in independent samples *t* test between two groups versus baseline. The data are presented as mean ± SD.

Our results are consistent with earlier works. The meta-analysis by Lippi et al found that increased serum PCT levels were associated with a nearly 5-fold higher risk of severe disease in patients affected by COVID-19. Moreover, the authors suggested that periodic assessment of the PCT level might be helpful in predicting the evolution of COVID-19 towards a more severe form (8). Vazzana et al found that increased PCT levels were more prevalent in patients with severe COVID-19 than in those with non-severe course (22.8% versus 5.8%) (OR, 5.92; 95% CI, 3.20 to 10.94), and patients with higher than normal PCT levels were more likely to have a poor outcome (44.0% versus 11.3%) (OR, 13.1; 95% CI, 7.37 to 23.1) (10). In another study, Hu et al investigated serum PCT in COVID-19 patients and found that it had increased in the deceased cases as their condition had become more severe. Therefore, the increase of serum PCT level can be a warning sign for severe forms of COVID-19 (11).

Procalcitonin is a glycoprotein with no hormonal activity, precursor of the hormone calcitonin (12). The serum PCT level in healthy people is lower than detectable, but its level increases as the result of systemic inflammations, especially during bacterial infections (7). In the presence of bacterial infection, the synthesis and release of PCT into the blood from sources other than thyroid increase considerably and actively continue with the increase of interleukin-1beta (IL-1β), tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6) concentrations (8). However, the synthesis of this biomarker is prohibited by interferon gamma (IFN-γ), whose concentration increases during viral infections (13). Therefore, PCT level is relatively lower in viral infections, which can be used to distinguish between bacterial and viral infections (14). In addition to serious bacterial infections, elevated PCT values can be found in critically-ill patients at increased risk of organ injury (15). In the present study, the mean PCT value in the enrolled severe to critically-ill patients was higher than normal. In line with this finding, Liu et al reported significantly higher levels of IL-6, C-reactive protein (CRP), and PCT in patients with severe COVID-19 than in those with milder forms, and showed that inflammatory factors play a key role in the progression of the disease from mild to severe forms (16).

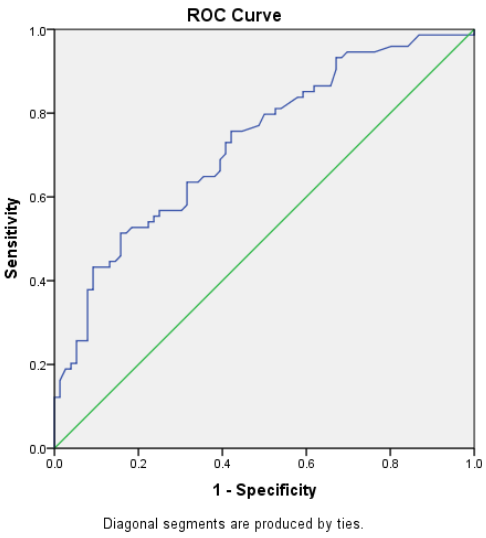

Figure 1. ROC curve.

Table 3. Area under the curve

Test Result Variable(s); Procalcitonin				
Area	Std. Error[a]	Asymptotic Sig[b]	Asymptotic 95% CI	
			Lower bound	Upper bound
0.727	0.041	0.000	0.717	1.03

Table 4. Binary logistic regression result

Variable	*P* value	Exp(B)
Procalcitonin	0.002	0.668
Urea	0.018	0.983
Cr	0.026	1.00

One potential reason for the higher serum PCT levels in patients with severe to critical COVID-19 might be the presence of a superimposed bacterial co-infection. According to previous studies, secondary bacterial infections in critically-ill COVID-19 patients occurred between 14 and 28% of case (17-19). Huang et al observed in their study that 4 of 41 patients, the patients hospitalized in ICU were afflicted with secondary infection, 3 of which had serum PCT levels higher than 0.5 ng/mL (20). They also showed that the increase in the level of this biomarker can be indicative of a poor prognosis.

Vanhomwegen et al assessed the values of PCT at admission to ICU in 66 critically-ill COVID-19 patients. They found a total of 7 (11%) patients who 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 ($P = 0.14$). The authors concluded that PCT is not reliable to diagnose bacterial co-infection in COVID-19 patients within 48 hours of admission (21).

In the present study, the presence of secondary bacterial infection was not assessed, and we were unable to explore the relationship between this complication and PCT levels in severe to critically-ill COVID-19 patients. To date, it remains unclear whether PCT levels in deteriorating COVID-19 patients are increased because of bacterial infections or hyperinflammatory state (cytokine storm) with target organ injury. As a consequence, it is still undefined if PCT may be used for detecting superimposed bacterial infections and guiding antibiotic therapy in COVID-19 patients (10).

Conclusion

Serum PCT levels were significantly associated with mortality in a cohort of COVID-19 patients admitted to ICU. Consequently, the PCT level could be used to early identify those patients at increased risk of complications and poor outcome who may benefit from timely and more intensive care management. Further investigation is needed to support this conclusion.

Limitations of the study

Limitations of the study are small number of patients, retrospective and monocentric design, which might limit its generalization.

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Authors' contribution

Conceptualization: AZ and SM. Methodology: AZ and SM. Investigation: AZ, SM and AF. Resources: AZ, SM and AF. Data Curation: AZ, SM and AF. Writing—Original Draft Preparation: AZ, SM and AF. Writing—Review and Editing: AZ, SM and AF. Supervision: AZ, SM and AF. Project Administration: AZ, SM and AF.

Data availability statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Ardabil university of medical sciences approved all study protocols (IR.ARUMS.REC.1399.088). The authors have entirely observed ethical issues (including plagiarism, data fabrication, and double publication).

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