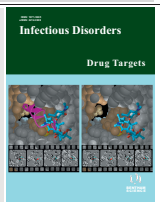
Infectious Disorders - Drug Targets, 2022, *22*, e070122200097

RESEARCH ARTICLE

Procalcitonin as a Prognostic Factor in Patients with COVID-19 in Southwestern Iran



Milad Shahini Shams Abadi[1,2], Elham Taheri[3], Ahmad Raesi[4], Mohammad-Hassan Arjmand[1,2], Soleiman Kheirii[5], Najmeh Shahinfard[2] and Zahra Habibi[2,*]

[1]*Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran;* [2]*Clinical Research Development Unit, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran;* [3]*Molecular Pathology and Cytogenetic Ward, Pathology Department, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran;* [4]*Department of Internal Medicine, Clinical Research Development Unit, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran;* [5]*Modeling in Health Research Center and School of Public Health, Department of Epidemiology and Biostatistics, Shahrekord University of Medical Sciences, Shahrekord, Iran*

ARTICLE HISTORY

Received: June 07, 2021
Revised: September 21, 2021
Accepted: October 20, 2021

DOI:
10.2174/1871526522666220107141109

Abstract: ***Background:*** There is increasing evidence supporting a central role of the viral-induced hyper-inflammatory immune response in the pathogenesis of COVID-19. Serum procalcitonin (PCT) is an emerging prognostic marker in coronavirus disease 2019 (COVID-19). The aim of this study was to investigate the relationship between serum procalcitonin and clinical severity and outcomes in patients with coronavirus disease 2019 (COVID-19).

Materials and Methods: Hematological and biochemical parameters were evaluated in patients with COVID-19 infection from February to April 2020 at Hajar Hospital in the Shahrekord University of Medical Science, Shahrekord, Iran.

Results: The results showed that total lymphocyte counts, albumin, calcium, and creatinine levels were significantly different between the two moderate and severe groups, and the mean of procalcitonin level in COVID-19 patients with severe disease was higher (0.36 ng/mL) compared with the patients with moderate disease, and its level was found to be >5 ng/mL in 14.2% of5 ng/mL in 14.2% of patients in the former group.

Conclusion: PCT may be a marker of disease severity in COVID-19 and may contribute to determining the severity of patients infected with SARS-CoV-2. Moreover, serial PCT measurements may be beneficial in predicting the prognosis.

Keywords: Procalcitonin, COVID-19, albumin, calcium, creatinine, prognosis.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is defined as an illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. It was first reported in December 2019 in Wuhan, China, and has spread globally since then, resulting in an ongoing pandemic [2].

Although most patients have mild symptoms and a good prognosis, the disease symptoms may deteriorate rapidly. It may present with Acute Respiratory Distress Syndrome (ARDS) and systemic inflammation [3, 4]. These patients usually need oxygen therapy and even ventilation assistance in the ICU. Despite intensive care measures, unfortunately, the mortality rate reaches as high as 60.5% in the severe form, *i.e.*, ARDS [3, 5].

Thus, to make a rapid assessment to assist clinical decisions, it is important to assess prognostic factors and evaluate the disease severity. Several laboratory tests have been suggested as prognostic factors, including viral load, lactic acid, lymphocyte count, CRP, IL – 6, IL-10, and procalcitonin [6, 7].

Procalcitonin (PCT) is a prohormone of calcitonin synthesized by thyroid neuroendocrine cells, but its biological function is different from calcitonin. Procalcitonin has emerged as a promising marker for identifying and monitoring patients with suspected and proven bacterial infections from other causes of infection or inflammation. Hence, PCT can serve as a helpful adjunct to determine clinical severity and to assess the response to antibiotic therapy [4]. Its normal level is quite low and is considered to be <0.1 ng/mL in healthy individuals [5]. Its synthesis is

*Address correspondence to this author at the Department of Internal Medicine, Clinical Research Development Unit, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran; Tel/Fax: +98 383336732; E-mail: dr_Z_habibi@yahoo.com

2212-3989/22 $65.00+.00

greatly up-regulated in the presence of bacterial infection or cytokines, including IL-6. A Procalcitonin plasma level of 0.2 ng/mL is a useful cut-off to rule out sepsis and systemic inflammation [5]. The effect of viral infection on procalcitonin contrasts with that of bacterial infections. Procalcitonin production is inhibited by interferon γ produced by T helper cells in viral infections [8, 9]. Therefore, elevated levels of serum procalcitonin have been proposed as a diagnostic biomarker to distinguish between bacterial and viral infections and is a prognostic marker and mortality index in sepsis [10]. Procalcitonin (PCT) testing on admission seems to be a valuable additional price of information to aid in early risk assessment and rule out bacterial co-infections in COVID-19 patients [11].

However, the value of procalcitonin plasma level in disease classification and prognosis remains undetermined. Therefore, this study was conducted to investigate the level of procalcitonin in COVID-19 patients in order to evaluate its prognostic value.

2. MATERIALS & METHODS

This observational study was carried out on adults ≥18 years of age who presented with COVID-19 infection from February through April 2020 admitted to Hajar Hospital in the Shahrekord University of Medical Science, Shahrekord, Iran, having a definite COVID-19 diagnosis due to a positive real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay on their nasopharyngeal swab specimens. Patients with chronic disease (hepatic or renal dysfunction) and cancer were excluded.

The clinical outcomes (such as mortality, organ injury, discharges) were monitored up to discharge or the death of patients up to April 26, 2020. The categories of the severity of the COVID-19 infection were according to the WHO-China joint mission. Mild: laboratory-confirmed, without pneumonia and imaging manifestations; Moderate: laboratory-confirmed and with fever, or respiratory tract infection symptoms and imaging indicating pneumonia; Severe: respiratory frequency ≥30 beats per minute (bpm), dyspnea, oxygen saturation (SpO2) ≤93%, PaO2/FiO2 ratio less than 300 mm Hg, lung infiltration>50% of the lungs on imaging. The patients within this group require ICU admission.

Demographic data were collected from electronic medical records, including sex, age, duration of hospitalization, and initial symptoms. The serum levels of calcium, Hemoglobin (HGB), Hematocrit (HCT), white blood cell (WBC), procalcitonin, and the lowest O2 saturation within 24 hours of admission were recorded. Although most data were extracted from electronic medical records, data on PCT were required for research purposes while these tests had not been performed for clinical purposes. These tests were performed using serum samples of patients who were systematically stored and then remained after diagnostic procedures. Therefore, there was no need to repeat the venipuncture and blood collection so that the patients were not embarrassed or presented additional risk or harm for research purposes. Consequently, implied consent of the patients obtained in clinical assessments has been assumed for this reuse. In addition, to protect the confidentiality and privacy of individuals, strategies such as coding during registry and data analysis have been used.

The data were summarized as percentages and frequencies for categorical variables and Means ± SD for continuous ones. Differences between variables among groups were analyzed using an independent sample T-test and chi-square test, if applicable. Logistic regression was used to calculate the odds ratios (OR) with confidence intervals at 95% for categorical outcomes. Analysis was performed by SPSS version 23 and STATA version 0.05, and statistical significance was defined as $p < 0.05$.

3. RESULTS

A total of 90 patients with confirmed COVID-19 were enrolled in this study. The mean age of patients was 55.3 years, and 54 (60%) were male. Of these patients, 49 (54.4%) were classified as severe. 15 (16.7%) of the patients died; all of them were in the severely affected group of COVID-19 patients. Selected Characteristics of the patients are shown in Table **1**. The mean serum procalcitonin level of COVID-19 patients was 0.24 ± 0.55. Overall, 49 patients of 90 patients enrolled in the study were classified as severe (54.4%). We had no patient belonging to the mild group. Total lymphocyte counts, albumin, calcium, and creatinine levels had a significant difference between the two moderate and severe groups (Table **2**). A ROC curve was used to assess the associations between serum procalcitonin and severity. Optimal cut-off points of serum procalcitonin values were derived from the ROC curves and are shown in Fig. (**1**). Evaluating the correlations between age and the value of Immunoglobulins, a direct association was observed between IgG and age (Pearson Correlation= 0.3 and *p*-value= 0.01), whereas age and IgM were not associated with each other's (Pearson Correlation= 0.16 and *p*-value= 0.2). However, regarding the absolute values for Ig tests, significant differences were observed; the mean serum IgM in severe patients was 6.1, while this value in moderate patients was 2.2 (p <0.001). Also, the mean of IgG was significantly more in severe patients than moderate ones (13.8 *vs*. 7.5, *p*-value <0.001). Regarding the rate of positive Immunoglobulins, there was no significant difference between severe and moderate groups. In the severe group, 94.7% patients had positive IgM, while this value was 85.7%% in

Table 1. Selected characteristics of COVID-19 patients.

Parameter	Mean ± SD / N (%)
Respiratory rate	21.8±5.9
Temperature	37.8938 ± .77400
O2SAT	86±11
Dyspnea	73.5
Cough	83.1
Death	15
ICU admission	21

Table 2. Some characteristics of COVID-19 patients based on clinical severity.

	Moderate (n=41)	Severe (n=49)	*p*-Value
Variable	Mean ± SD / N (%)	Mean ± SD / N (%)	
Age (year)	49.7±15.5	60.2±16.8	0.003
Hospitalization (day)	6.4±2	8.5±3.4	0.001
Respiratory rate	19.5±3	23.5±6.9	0.001
O2 saturation	91.5±5	82.1±12.4	0.001
White Blood Cell	6719.5±3526.2	7834.7±5266.2	0.235
Lymphocyte	1312.2±554.6	1022.9±584.9	0.018
Hemoglobin (g/dL)	14.1±1.8	13.9±2.05	0.702
Albumin (g/dL)	3.9±0.4	3.6±0.5	0.010
Calcium (mg/dL)	8.6±0.4	7.8±0.6	0.001
BUN (mg/dL)	14.1±6.9	18.6±12.2	0.034
Creatinine (mg/dL)	0.78±0.15	0.98±0.47	0.007
Sodium (mmol/L)	137.8±2.6	136.5±3.6	0.053
Potassium (mmol/L)	4.12±0.4	4.05±0.4	0.362
Procalcitonin (ng/mL)	0.0654±0.066	0.3661±0.686	0.007

Statistical significance at $P < 0.05$.

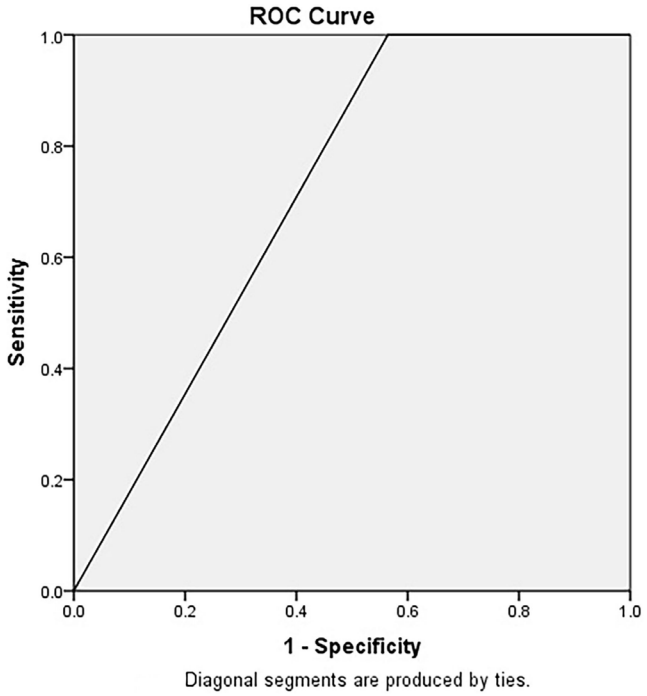


Fig. (1). ROC curve for the associations between serum procalcitonin and severity in patients with Covid-19 (area under the curve: 0.718). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

moderate group (*p*-value= 0.34). Also, 91.7% had positive IgG in the severe group, while this value was 91% in the moderate group (*p*-value= 0.4). Fifty-seven patients from 91 patients had a report for IgM and IgG serologic tests for COVID_19. For 87.7% of the patients, both tests were positive; For 8.8% of patients, both tests were negative; 3.5% had the positive result for IgG and negative result for IgM. The mean values of Immunoglobulins were not significantly different between two gender groups of patients; the values for IgM were 4.9 in males *vs*. 4.3 in females (*p*-value=0.5); those values for IgG were 12.32 *vs*. 10.26, respectively (*p*-value=0.2).

4. DISCUSSION

The frequency of raised (>0.5 ng/mL) procalcitonin level in COVID-19 patients at admission in this study was 10 %, and the average level was 0.2 ng/mL, while the mean level of procalcitonin in severe patients was 0.37 ng/mL. Hu *et al*. reported the mean range of procalcitonin in severe COVID-19 patients 0.5 ng/ml [11]. In a cohort study on 1099 Chinese COVID-19 patients, this frequency has also been reported as 5.5 %, and most COVID -19 patients had a procalcitonin level below 0.2 ng/mL [8, 12]. A meta-analysis also demonstrated that increased PCT values are related to an ~5-fold higher risk of severe COVID-19.

In this study, all patients with moderate disease severity and absence of adverse outcomes such as ICU admission, the requirement for mechanical ventilation, or death had low procalcitonin levels with an average mean of about 0.06 ng/mL. This finding was similar to the previous viral epidemics such as influenza H_1N_1, SARS, and MERS, in which the procalcitonin level was usually low (< 0.5 mg/L) in 96 % of hospitalized patients with pure viral infections [13, 14]. We found that the mean of the serum procalcitonin lev-

el in COVID-19 patients with severe disease was high (0.36 ng/mL) compared to the patients with moderate disease, and its level was found to be more than 5 ng/mL in 14.2% of patients in the former group. This difference in the procalcitonin level between the two severe and moderate groups was statistically significant. Several Studies from China have reported elevated procalcitonin levels (>0.5 ng/mL) in 6-30% of patients with COVID-19, and two of them correlated the procalcitonin level with the severity of disease or the risk of death [15, 16]. Therefore, performing this test at the time of admission appears to provide additional information to assess the early risk, and procalcitonin level monitoring can be helpful in diagnosing disease progression at an early stage. PCT may be an indicator of disease severity in COVID-19 and may contribute to determining the severity of patients infected with SARS-CoV-2. In terms of mortality, 57.1% of patients with high levels of procalcitonin (>0.5 ng/mL) died while 145.% of patients with low levels of procalcitonin died (OR= 7.85, 95% CI: 1.5-41.1, *P*-value=0.015).

Some additional laboratory findings and clinical assessments are used to evaluate the risk of severity and progression as well as monitoring therapeutic intervention such as lymphocyte count and IL-6, IL-10 [6]. In this study, total lymphocyte counts, albumin, calcium, and creatinine levels had a significant difference between the two moderate and severe groups. Hypocalcemia is common in critically ill patients. The causes of hypocalcemia include over secretion of PTH, Vit D deficiency, decreased dietary intake, hypoproteinemia, hypomagnesemia drug interactions, and so on [17]. Hypocalcemia was defined as a serum calcium level less than 2.2 mmol/L in our clinical laboratory. This means that patients with lower total lymphocyte counts, albumin, and calcium levels and higher creatinine levels at the time of admission have a worse prognosis. Other laboratory abnormalities findings in severe COVID-19 patients included hypoalbuminemia, lymphopenia, and elevation of inflammatory mediators (CRP, PCT, and IL-6) and concentrations of D-dimer [18-20]. These laboratory abnormalities are similar to previously published articles. Renal compromise and its effect on vitamin-D production and renin-angiotensin-aldosterone axis may implicitly justify lower calcium and potassium levels in severe cases with the higher creatinine level. Therefore, it can be considered a predisposing factor for the severe form of the disease. Additionally, albumin is a negative acute-phase reactant, and its lower level seems logical in patients with severe disease. Our study has several weaknesses: first, because of our small sample size, our results may be difficult to interpret, and the accuracy should be confirmed by large-scale clinical prospective studies. Secondly, because the study was not based on pathophysiological models, further research is needed to establish the exact relationship between PCT level and severity by more basic experiments. Furthermore, our findings may not be representative of other areas of Iran or other countries.

CONCLUSION

In spite of the several limitations, the results of this study showed that PCT may be an indicator of disease severity and may contribute to determining the severity of patients with COVID-19. In addition, initially elevated PCT levels may be used as a prompt prognosticator of criticalness, deteriorating clinical picture, and even mortality in COVID-19. However, additional investigation is needed to expansively evaluate the prognostic utility of PCT.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethical board of Shahrekord University of medical sciences with the number IR.SKUMS.REC.1398.051.

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. The procedures in this study were conducted in accordance with the ethical standards of the committee responsible for human experimentation in accordance with the Helsinki Declaration.

CONSENT FOR PUBLICATION

Participant willingly submitted their consents for publication of this study.

STANDARDS OF REPORTING

This study has been conducted under STROBE guidelines.

AVAILABILITY OF DATA AND MATERIALS

The data associated with this paper are available.

FUNDING

This study was financially supported by the research deputy of the Shahrekord University of Medical Sciences (Grant No: 3063).

CONFLICT OF INTEREST

The authors declare that no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Laing AG, Lorenc A, Del Molino Del Barrio I, *et al.* A dynamic COVID-19 immune signature includes associations with poor prognosis. Nat Med 2020; 26(10): 1623-35. http://dx.doi.org/10.1038/s41591-020-1038-6 PMID: 32807934

[2] Guo W, Li M, Dong Y, *et al.* Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020; e3319: e3319. http://dx.doi.org/10.1002/dmrr.3319 PMID: 32233013

[3] Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E. Prediction models for diagnosis and prognosis of covid-19: Systematic review and critical appraisal. BMJ 2020; 369.

[4] Qu R, Ling Y, Zhang YH, *et al.* Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol 2020; 92(9): 1533-41. http://dx.doi.org/10.1002/jmv.25767 PMID: 32181903

[5] van Berkel M, Kox M, Frenzel T, Pickkers P, Schouten J. Biomarkers for antimicrobial stewardship: a reappraisal in COVID-19 times? Crit Care 2020; 24(1): 600.

http://dx.doi.org/10.1186/s13054-020-03291-w PMID: 33023606

[6] Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun 2020; 111: 102452. http://dx.doi.org/10.1016/j.jaut.2020.102452 PMID: 32291137

[7] Shahini Shams Abadi M, Siadat SD, Vaziri F, *et al.* Distribution and diversity of hmw1A among invasive nontypeable haemophilus influenzae isolates in Iran. Avicenna J Med Biotechnol 2016; 8(2): 99-102.
PMID: 27141269

[8] Zhao Z, Chen A, Hou W, *et al.* Prediction model and risk scores of ICU admission and mortality in COVID-19. PLoS One 2020; 15(7): e0236618.
http://dx.doi.org/10.1371/journal.pone.0236618 PMID: 32730358

[9] Heesom L, Rehnberg L, Nasim-Mohi M, *et al.* Procalcitonin as an antibiotic stewardship tool in COVID-19 patients in the intensive care unit. J Glob Antimicrob Resist 2020; 22: 782-4.
http://dx.doi.org/10.1016/j.jgar.2020.07.017 PMID: 32717489

[10] Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. Int J Antimicrob Agents 2020; 56(2): 106051.
http://dx.doi.org/10.1016/j.ijantimicag.2020.106051 PMID: 32534186

[11] Zhou B, She J, Wang Y, Ma X. Utility of ferritin, procalcitonin, and C-reactive protein in severe patients with 2019 novel coronavirus disease. Research Square 2020.
http://dx.doi.org/10.21203/rs.3.rs-18079/v1

[12] Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis 2020; 14: 1753466620937175.
http://dx.doi.org/10.1177/1753466620937175 PMID: 32615866

[13] Zhang YY, Li BR, Ning BT. The comparative immunological characteristics of SARS-CoV, MERS-CoV, and SARS-CoV-2 coronavirus infections. Front Immunol 2020; 11: 2033.
http://dx.doi.org/10.3389/fimmu.2020.02033 PMID: 32922406

[14] Liya G, Yuguang W, Jian L, *et al.* Studies on viral pneumonia related to novel coronavirus SARS-CoV-2, SARS-CoV, and MERS-CoV: a literature review. APMIS 2020; 128(6): 423-32.
http://dx.doi.org/10.1111/apm.13047 PMID: 32363707

[15] Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chim Acta 2020; 505: 190-1.

[16] Liu F, Li L, Xu M, *et al.* Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol 2020; 127: 104370.
http://dx.doi.org/10.1016/j.jcv.2020.104370 PMID: 32344321

[17] Kelly A, Levine MA. Hypocalcemia in the critically ill patient. J Intensive Care Med 2013; 28(3): 166-77.
http://dx.doi.org/10.1177/0885066611411543 PMID: 21841146

[18] Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497-506.
http://dx.doi.org/10.1016/S0140-6736(20)30183-5 PMID: 31986264

[19] Wang D, Hu B, Hu C, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020; 323(11): 1061-9.
http://dx.doi.org/10.1001/jama.2020.1585 PMID: 32031570

[20] Chen N, Zhou M, Dong X, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223): 507-13.
http://dx.doi.org/10.1016/S0140-6736(20)30211-7 PMID: 32007143

HOW TO CITE:

Milad Shahini Shams Abadi, Elham Taheri, Ahmad Raesi, Mohammad-Hassan Arjmand, Soleiman Kheirii, Najmeh Shahinfard and Zahra Habibi*, "Procalcitonin as a Prognostic Factor in Patients with COVID-19 in Southwestern Iran", *Infectious Disorders - Drug Targets* 2022; *22*(3): e070122200097