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Procalcitonin and C-Reactive protein levels among COVID-19 patients in Sulaymaniyah Governorate

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Abstract

COVID-19 is a viral disease that affects multiple body organs. The objective of this study is Investigating the role of PCT and CRP in predicting the outcome of patients with COVID-19. Cross-sectional prospective study including 135 patients with SARS-CoV-2 confirmed by RT-PCR. Serum level of PCT and CRP are measured at admission and on day 10 post-admission. Patients are followed up for one month. The mean level of PCT on day 1 was 0.1±0.28 ng/ml compared with 0.3±1.27 ng/ml on day 10. Respectively, the mean serum level of CRP on day 1 and day 10 was 113.57±89.88mg/L and 44.76±43.29 mg/L. At admission, the mean serum level of PCT and CRP in dead patients was 0.22±0.6 ng/ml and 164.0±105.59 mg/L, respectively compared with 0.07±0.08 ng/ml and 101.42±82.03 mg/L, respectively in the survived group. After 10 days of admission, the median serum level of PCT and CRP in dead patients was 1.5±2.74 ng/ml and 70.9±57.87 mg/L. respectively compared with 0.13±0.23 ng/ml and 37.7±34.87 mg/L, respectively in the survived patients. In conclusion, the serum level of PCT and CRP increases from admission to day 10 post-admission, and they are considered as indicators of severe inflammatory response and could increase mortality risk.

Keywords: SARS, SARS-COV-2, RT-PCR, Procalcitonin (PCT), C-CRP

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has caused a sudden significant increase in hospitalizations for pneumonia with the multiorgan disease. COVID-19 is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infection may be asymptomatic, or it may cause a wide spectrum of symptoms, such as mild symptoms of upper respiratory tract infection and life-threatening sepsis [1]. Although reported COVID-19 deaths between Jan 1, 2020, and Dec 31, 2021, totaled 5·94 million worldwide, we estimate that 18·2 million (95% uncertainty interval 17·1–19·6) people died worldwide because of the COVID-19 pandemic (as measured by excess mortality) over that period. The global all-age rate of excess mortality due to the COVID-19 pandemic was 120·3 deaths (113·1–129·3) per 100 000 of the population, and excess mortality rate exceeded 300 deaths per 100 000 of the population in 21 countries. The number of excess deaths due to COVID-19 was largest in the regions of South Asia, North Africa and the Middle East, and Eastern Europe [2].

SARS-CoV-2 uses the same receptor as SARS-CoV-1, angiotensin-converting enzyme 2 (ACE2) [3]. Besides human ACE2 (hACE2), SARS-CoV-2 also recognizes ACE2 from pig, ferret, rhesus monkey, civet, cat, pangolin, rabbit and dog [4]. The broad receptor usage of SARS-CoV-2 implies that it may have a wide host range, and the varied efficiency of ACE2 usage in different animals may indicate their different susceptibilities to SARS-CoV-2 infection [5]

The S1 subunit of a coronavirus is further divided into two functional domains, an N-terminal domain and a C-terminal domain. Structural and biochemical analyses identified a 211 amino acid region (amino acids 319–529) at the S1 C-terminal domain of SARS-CoV-2 as the receptor binding domain (RBD), which has a key role in virus entry and is the target of neutralizing antibodies [6]. This domain contacts with the ACE2 receptor. Interestingly, this region in SARS-CoV-2 differs from that in SARS-CoV-1 in five amino acids which are Y455L, L486F, N493Q, D494S and T501N. These amino acids are important in the binding with ACE2 [7].

Owing to these residue changes, interaction of SARS-CoV-2 with its receptor stabilizes the virus on the surface of hACE2. Moreover, a four-residue motif in the RBD of SARS-CoV-2 (amino acids 482–485) results in a more compact conformation of its hACE2-binding ridge than in SARS-CoV-1 and enables better contact with the N-terminal helix of hACE2 [6]. Biochemical data confirmed that the structural features of the SARS-CoV-2 RBD have strengthened its hACE2 binding affinity compared with that of SARS-CoV [8].

Similar to other coronaviruses, SARS-CoV-2 needs proteolytic processing of the S protein to activate the endocytic route. It has been shown that host proteases participate in the cleavage of the S protein and activate the entry of SARS-CoV-2, including transmembrane protease serine protease 2 (TMPRSS2), cathepsin L and furin [9]. Single-cell RNA sequencing data showed that TMPRSS2 is highly expressed in several tissues and body sites and is co-expressed with ACE2 in nasal epithelial cells, lungs and bronchial branches, which explains some of the tissue tropism of SARS-CoV-2 [10,11].

SARS-CoV-2 pseudovirus entry assays revealed that TMPRSS2 and cathepsin L have cumulative effects with furin on activating virus entry. Analysis of the cryo-electron microscopy structure of SARS-CoV-2 S protein revealed that its RBD is mostly in the lying-down state, whereas the SARS-CoV S protein assumes equally standing-up and lying-down conformational states. A lying-down conformation of the SARS-CoV-2 S proteins may not be in favor of receptor binding but is helpful for immune evasion [12].

The pathogenesis of SARS-CoV-2 infection in humans manifests itself as mild symptoms to severe respiratory failure. On binding to epithelial cells in the respiratory tract, SARS-CoV-2 starts replicating and migrating down to the airways and enters alveolar epithelial cells in the lungs [13]. The rapid replication of SARS-CoV-2 in the lungs may trigger a strong immune response. Cytokine storm syndrome causes acute respiratory distress syndrome and respiratory failure, which is considered the main cause of death in patients with COVID-19 [14]. Patients of older age (>60 years) and with serious pre-existing diseases have a greater risk of developing acute respiratory distress syndrome and death [15]. Multiple organ failure has also been reported in some COVID-19 cases [16].

According to the clinical manifestations, confirmed patients are divided into mild, moderate, severe, and critical types (Table 1-1).

Table 1.

Criteria for Clinical Severity of Confirmed COVID- 19 [17]

Type	**Finding**
Mild	Mild clinical symptoms [fever <38℃(decreased without treatment), with or without cough, no dyspnea, no gasping, no chronic disease] No imaging findings of pneumonia
Moderate	Fever, respiratory symptoms, imaging findings of pneumonia
Severe	Meet any of the followings: a. Respiratory distress, RR ≥30 times/min b. SpO2 <93% at rest c. PaO2/FiO2 ≤ 300 mmHg Patients showing a rapid progression (>50%) on CT imaging within 24- 48 hours should be managed as severe
Critical	Meet any of the followings: a. Respiratory failure, need mechanical assistance b. Shock c. Extrapulmonary organ failure, intensive care unit is needed

FiO2 = fraction of inspired oxygen, PaO2 = partial pressure of oxygen, RR = respiratory rate, SpO2 = oxygen saturation.

The COVID-19 infection starts by exposure to microdroplets present in the exhalations of infected individuals. Then, the SARS-CoV-2 spreads to the bronchioles and alveolar spaces [18], entrancing into the host cells (e.g., endothelial, epithelial, and smooth muscle cells) by binding the angiotensin-converting enzyme (ACE)-2, a metallopeptidase present on the cell surface [3].

In the lung, SARS-CoV-2 infects the alveolar cells (type I and II pneumocytes and alveolar macrophages) and then starts intracellular replication in pulmonary tissues. Type I and III interferons (IFN) production is an early defense mechanism in the alveolar cells [18].

However, researchers have found deficient expression of these cytokines, besides the upregulated expression of chemokines and interleukins [19]. In normal human bronchial epithelial cells culture, the cytokine profile includes the IFNs deficiency and elevated expression of CCL20, CXC-type chemokines, IL-1β, IL-6, and tumor necrosis factor (TNF). The type I and III IFN absence shows that, although SARS-CoV-2 is sensitive to IFN antiviral effect, the virus can inhibit its induction [20]. This ability may come from, at least, one mechanism of blocking the activation of the IFN signaling pathway at an early step following the nuclear transport of interferon regulatory factors (IRF) [21]. Furthermore, the recruitment of leukocytes, a hallmark of inflammation, is strongly related to the chemokine profile. For example, CCL2 and CCL8 recruit monocytes/macrophages, CXCL16 is a chemoattractant of NK cells, and CXCL8 is the principal neutrophil chemoattractant, and CXCL9 and CXCL10 chemoattract T cells. Thus, the chemokine profile may be a driver of the signature pathology of SARSCoV-2 [22].

The immune features between moderate and severe disease are modified after ten days of infection when severely ill patients remain with high proinflammatory cytokines [23]. Furthermore, deregulated inflammatory response to an infection may result in the cytokine storm syndrome, which is associated with severe COVID-19 [24]. This syndrome is characterized by high levels of interleukins, TNF-α, G-CSF, MCP-1, and MIP-1α, which are higher in intensive care unit (ICU) patients than non-ICU patients [23]. Additionally, the inflammasome NLRP3, a multiprotein complex crucial to the host defense, is highly activated in COVID-19 patients. Inflammasome-induced cytokines IL-1β and IL-18 also contribute to cytokine storm, and sustained NLRP3 inflammasome activation is directly associated with the disease's severity [25].

Peripheral blood immune cells (PBMCs) of COVID-19 patients present low T cell number and frequency in both CD4+ and CD8+ populations, which are more activated. On the order hand, monocytes are increased [17]. Additionally, in severe COVID-19, patients present a reduced number of B cells and natural killer (NK) cells associated with severe T cell depletion, and a high neutrophil population. This neutrophilia occurs after seven days symptoms onset [26].

C-reactive protein is an inflammatory protein of the pentraxin family and is produced in response to the acute inflammatory phase. Transcriptional induction of the CRP gene primarily occurs in hepatocytes in response to increased levels of inflammatory cytokines, especially interleukin-6 (IL-6) with IL-1 enhancing the effect [27]. C-reactive protein shows high expression during inflammatory conditions such as rheumatoid arthritis, some cardiovascular diseases and infection [28]. There are many factors that can alter CRP levels, including age, sex, smoking status, weight, lipid levels and blood pressure [29].

The increase of CRP in infections occurs mainly in bacterial infections; however, it cannot identify the type of bacterial infection [30]. The main role of CRP in bacterial inflammation tends to centre on the activation of the complement molecule C1q leading to opsonisation of pathogens. In the presence of calcium, CRP binds to polysaccharides such as phosphocholine on the microorganisms and triggers complement activation by the classical pathway activating C1q. In addition, CRP binds to Fc receptors on the cell surface leading to the release of pro-inflammatory cytokines. Thus, CRP is not only a marker of inflammation, but also contributes to the inflammatory response. Regarding to increased levels of CRP in SARS-CoV-2 infection, high levels of CRP have been associated with mortality from this infection. CRP has been identified as a molecule capable of causing damage during SARS-CoV-2 infection [31].

The pathogenesis of CRP is mediated by its isoform types. CRP has three different isoforms, native CRP (nCRP), monomeric (mCPR) and mixed isoform (mCRPm). In this respect, the nCRP is the native protein that is formed by five monomers (penta-monomeric) [32]. This molecule presents two ligands at opposite sides of the molecule, one of which binds calcium and the other interacts with the C1q of the complement and with Fc receptors [28]. This isoform is synthesized mainly in the liver but is also synthesized by other cells such as endothelial cells, macrophages, lymphocytes, muscle cells and adipocytes [33]. This form is stored in the endoplasmic reticulum and is slowly released into the circulation, except in states of inflammation, where it is rapidly eliminated to the circulation by the action of pro-inflammatory cytokines. The nCRP dissociates and gives rise to monomers (mCRP). These two isoforms have different biological properties during the inflammatory process, a phenomenon related to the points where the ligands of each molecule join [34]. There is a third isoform, mCRPm, which originates when nCRP partially dissociates and leaves an isoform that retains part of nCRP. This occurs when nCRP is bound to the cell membrane, leaving mCRPm with a high capacity to activate complement [31].

C-reactive protein has been used for a long time as an indicator of acute phase inflammation; however, in the current Covid-19 pandemic it is related to tissue damage and poor prognosis of the disease. In this regard, high levels of CRP in the early stage of Covid-19 have been associated with lung damage and the severity of the disease [35]. Analysis of lung alterations assessed by computerized tomography (CT) shows that high levels of CRP are present before

the appearance of lung lesions, giving to CRP predictive values of severity [36]. The progression to pneumonia has been associated with the increased circulating CRP levels [37]. Studies involving CRP levels and respiratory function showed inverse correlation between elevated CRP levels with decreased partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO2/FiO2), suggesting that CRP is a predictor factor of lung failure [38]. Other studies show the association of CRP with other parameters in the evolution of Covid-19. In this context, high levels of CRP with low levels of albumin have been associated with poor prognosis and increased mortality [39].

CRP induces apoptosis by several mechanisms: (1) induction of pro-apoptotic cytokines such as TNF-α and IL-1-β and induction of reactive oxygen species through activation of Fc-γ receptors [40]. (2) Induction of p53 up-regulation altering the cell cycle through activation of Fc-γRII [41]. (3) Activation of genes related to the expression of adhesion molecules and chemotactic cytokines. (4) Induction of GADD153 gene expression related to cell cycle arrest and DNA damage. (5) Activation of caspase-370 which additionally promotes the opsonisation of apoptotic cells [31]

Procalcitonin (PCT) is a 116-amino acid peptide with a molecular weight of 14.5 kDa. It consists of three sections: the amino terminus (57 amino acids), immature calcitonin (33 amino acids) and calcitonin carboxyl-terminus peptide 1 (CCP-1) also known as katacalcin (21 amino acids). Its production is governed by the calcitonin 1 gene (CALC-1) on chromosome 11. The product of this gene, prePCT, undergoes proteolytic cleavage producing PCT, which is further processed to the mature calcitonin molecule. Transcription and translation of CALC-1 gene is normally confined to the thyroid C-cells and, to a lesser extent other neuroendocrine cells [42]. Production is, however, activated in all parenchymal tissues in response to bacterial infection, mediated by cytokines interleukin-6 (IL6), tumour necrosis factor-α (TNF-α) and interleukin-1β (ILβ). Conversely, PCT production is attenuated by interferon-γ primarily secreted in response to viral infection [43].

Factors which may cause a raised PCT apart from a bacterial infection include recent major surgery [44], severe trauma [45], severe burns [46], and prolonged cardiogenic shock [47]. However, in the absence of infection, these patients should have decreased PCT levels on subsequent measurements.

Patients on medications which stimulate cytokine release such as OKT3, antilymphocyte globulins, alemtuzumab, IL-2 and granulocyte transfusion will also have an elevated PCT level [48]. Dysregulated PCT production leading to a high PCT is seen in patients with paraneoplastic syndromes due to medullary thyroid and small cell lung carcinomas [49].

PCT is a biomarker of systemic inflammatory activity in the early phase after infection resulting from pro-inflammatory stimuli which are bound up with the prognosis of infectious diseases [50]. Furthermore, studies have reported that PCT is associated with the severity of COVID-19 [51, 52]. A retrospective study suggested that PCT was a risk factor of in-hospital death

from COVID-19 (OR = 6.350, 95% CI: 1.396–28.882) [53]. However, it was worth noting that PCT was considered as an important risk factor of the severity of COVID-19 based on univariate analysis (OR = 1.13, 95% CI: 1.03–1.24), which is inconsistent with those based on multivariate analysis after adjusting for confounding factors (OR = 1.05, 95% CI: 0.96–1.15) [54]. It suggested that the association between PCT and the severity of COVID-19 might be confounded by some confounding factors. In a meta-analysis including 10 studies with a total of 7716 patients, PCT on admission was found to be positively associated with the severity of COVID-19 (OR= 1.77, 95% CI: 1.38–2.29), and the relationship also existed between elevated PCT on admission and dead patients (OR= 1.77, 95% CI: 1.36–2.30) even after controlling the confounders [55].

The aim of this study is to investigate the role of PCT and CRP in predicting the outcome of patients with COVID-19.

Materials and Methods

This is a cross-sectional prospective study including (135) patients with SARS-CoV-2 who were admitted and treated at Shaheed Dr. Hemin Teaching Hospital in Sulaimaniyah city during the period from 1st January 2021 to 1st February 2022. Patients were diagnosed by high resolution computed tomography (HRCT) of the chest with no other explanation of the symptoms (i.e. bacterial infection), and were confirmed by Nasopharyngeal swab examination of SARS-CoV-2 RNA by real-time polymerase chain reaction.

All patients with age ≥ 18 years, confirmed with SARS-CoV-2 infection, with moderate to severe COVID-19 infection were included whereas patients who refused to participate in the study were excluded.

Approval was taken from the scientific council of the Arab Board of Health Specializations in Ira and from the authority of the Shaheed Dr. Hemin Teaching Hospital. A written consent from each participant was obtained prior to data collection after explaining the aim of study. Each patient is given complete unconditioned choice to withdraw anytime. The confidentiality of data throughout the study was guaranteed and the patients were assured that data will be used for research purposes only.

A questionnaire used to include Patients' demographics (age, gender, address, smoking status, and Tel. number) comorbidities, chief complaints, and clinical manifestations were collected through direct interview. PCT and CRP were gathered from patient records, PCT and CRP were measured on the first day of admission and after 10 days of admission. Pulmonary CT scan findings, SPO_2, and vital signs were measured at admission.

Patients were followed up for one month after admission, during which the mortality rate was reported. According, patients were divided into two broad categories: survived and non-

survived. The association of different demographic, clinical, and laboratory characteristics with the survival rate was calculated.

The quantitative data were expressed as mean ± standard deviation. Binomial data were presented as frequency percentages. Comparisons between quantitative were performed by the parametric Student *t*-test, while the comparison between binomial data was done by the Chi-square test. All data were analyzed with SPSS for Windows, v.25.0, IBM Corp, Armonk, New York, USA.

Results

The mean age of the patients was 56.59± 15.93 years (range 20-87 years), with more than half of them 75(55.55%) males and 60(44.44%) females. Hypertension and DM were common comorbidities accounting for 37.78% and 23.7% of the patients, respectively. Only a small percentage 13(9.63%) of the patients were smokers (Table 1).

Table 1.

Demographic characteristics of the Patients (n=135)

Variables	**Values**
Age, years	
Mean±SD	56.59± 15.93
Range	20-87
Gender	N (%)
Male	75(55.55)
Female	60(44.44)
Comorbidities	
No comorbidities	77(57.04)
Hypertension	51(37.78)
Type 2 diabetes mellitus	33(23.7)
Ischemic heart disease	7(5.19)
Heart failure	6(4.44)
Malignancy	4(2.96)
CVA	3(2.22)
COPD	2(1.48)
Others	15(11.11)
Smoking	N (%)
No smoking	122(90.87)
Smoking	13(9.63)

Shortness of breath was the most common symptom affecting 121(89.63%) of the patients followed by myalgia 104(77.04%), cough 100(74.07%) fatigue 100(74.07%), and loss of taste 94(69.63%). Less commonly reported are insomnia 48(35.56%), headache 47(34.81%), fever 40(29.63%), loss of smell 33(24.44%), sore throat 24(17.78%), diarrhea 23(17.04%), sweating 20(14.81%), vomiting 19(14.07%) and constipation 18(13.33%). Lung involvement was greater than 50% in 84(37.78%).

Table 2.

Clinical features and lung involvement on CT scan (n=135)

Variables	**N (%)**
Clinical Features	
Shortness of breath	121(89.63)
Myalgia	104(77.04)
Cough	100(74.07)
Fatigue	100(74.07)
Taste loss	94(69.63)
Insomnia	48(35.56)
Headache	47(34.81)
Fever	40(29.63)
Loss of smell	33(24.44)
Sore throat	24(17.78)
Diarrhea	23(17.04)
Sweating	20(14.81)
Vomiting	19(14.07)
Constipation	18(13.33)
Lung involvement according to CT	
≤50%	84(62.22)
>50%	51(37.78)

The mean Saturated PO_2 in the patients was 85.57±7.28%. The mean RR, PR and temperature were 30.23±9.48 breaths/min, 89.69±16.16.92 beats/min, and 37.14±1.06 °C respectively. While the mean SBP and DBP were 128.46±20.768 mmHg and 75.94±12.549 mmHg, respectively.

Table 3.

Vital signs (n=135)

Variables	Values
SPO_2, %	
Mean±SD	85.577.28
Range	60-99
Respiratory rate, breaths/min	
Mean±SD	30.23±9.48
Range	15-50
Pulse rate, beats/min	
Mean±SD	89.69±16.92
Range	51-153
Temperature, ^oC	
Mean±SD	37.14±1.06
Range	36.1-40.5
Systolic blood pressure, mmHg	
Mean±SD	128.46±20.768
Range	70-195
Diastolic blood pressure, mmHg	
Mean±SD	75.94±12.549
Range	50-110

Each PCT and CRP were recorded at admission (day 1) and 10 days after admission. Data regarding these markers were subjected for normality test and were found to be normally distributed. Thus, these data were presented as mean, standard deviation and, range) and analyzed with a non-parametric Wilcoxon Matched pair signed-rank test. The mean serum level of PCT at day 1 was 0.1±0.28 ng/ml which was lower than that at day 10 (0.3±1.27 ng/ml) with significant difference and the mean serum level of CRP at day 1 was 113.57±89.88 mg/L which was higher compared with that at day 10 (44.76±43.29 mg/L) with a significant difference as shown in Table 4.

Table 4.

PCT and CRP measurements on days 1 and 10 after admission

Markers	Day 1	Day 10	p-value
PCT, ng/ml			
Mean±SD	0.1±0.28	0.3±1.27	0.749
Range	0.02-3.21	0.02-12.79	
CRP, mg/L			
Mean±SD	113.57±89.88	44.76±43.29	**<0.001**
Range	7.1-380	1.32-147.08	

Regarding survival rate after a thirty-day follow-up, 108 (80%) of the patients survived, while 27 (20%) died as shown in Figure 1.

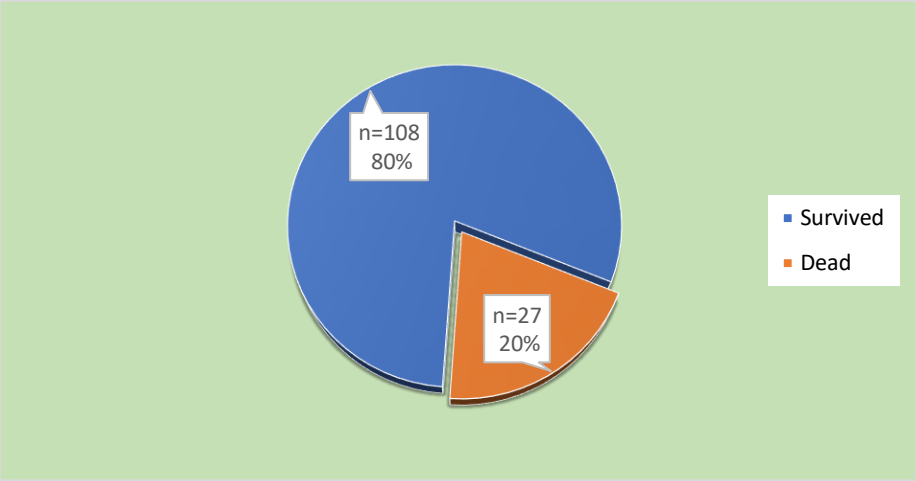

Figure 1.

Survival rate

Four factors, age, diabetes, malignancy, and CVA displayed a significant association with the survival rate. The mean age of the survived patients was 55.0±16.05 years which was lower than that of non-survived patients (62.89±13.97 years) with a significant difference (p = 0.038). Diabetes was more common among the deceased (40.74%) than the survived patients (20.37%) with significant differences. All patients with malignancy and CVA have died with highly significant differences as shown in Table 5.

Table 5.

Association of patients' characteristics and demographic data with the survival rate

Variables	**Survived(n=108) N (%)**	**died(n=27) N (%)**	**p-value**
Age, years Mean±SD	55.0±16.05	62.89±13.97	**0.021**†
Gender	N (%)	N (%)	
Male	57(56.07)	18(71.43)	0.194⁑
Female	51(43.93)	9(28.57)	
Smoking			
No smoking	100(92.59)	22(81.48)	0.080⁑
Smoking	8(7.41)	5(18.52)	
Comorbidities			
No comorbidities	68(62.96)	9(33.33)	**0.005**⁑
Hypertension	37(34.26)	14(51.85)	0.092
Type 2 diabetes mellitus	22(20.37)	11(40.74)	**0.028**
Ischemic heart disease	5(4.82)	2(7.41)	0.560
Heart failure	4(3.7)	2(7.4)	0339
Malignancy	0(0)	4(14.81)	**<0.001**
CVA	0(0)	3(11.11)	**<0.001**
COPD	1(0.92)	1(3.7)	0.285
Others	10(9.25)	5(18.5)	0.085

Out of all clinical features, the presence of shortness of breath (SOB) was the only clinical feature that is significantly associated with the survival rate. 25(92.59%) of non-survived had shortness of breath. 35(32.40%) of survived patients had lung involvement >50% compared with 73(67.59%) of the survived patients who had ≤50% lung involvement on HRCT as demonstrated in Table 6.

Table 6.

Association of clinical features and lung involvement according to HRCT survived and non-survived

Variables	**Survived (n=108) N (%)**	**Died (n=27) N (%)**	**p-value**
Clinical Features			
Shortness of breath	96(88.88)	25(92.59)	0.204
Myalgia	86(79.63)	18(66.67)	0.152
Cough	80(74.07)	20(74.07)	0.954
Fatigue	79(73.15)	21(77.78)	0.152
Taste loss	74(68.52)		0.623
Insomnia	40(37.04)	20(74.07)	0.472
Headache	36(33.33)	8(29.63)	0.574
Fever	33(30.56)	11(40.74)	0.470
Loss of smell	26(24.07)	7(25.93)	0.637
Sore throat	22(20.37)	7(25.93)	0.841
Diarrhea	20(18.52)	3(11.11)	0.268
Sweating	19(17.59)	3(11.11)	0.360
Vomiting	15(13.89)	1(3.7)	0.069
Constipation	16(14.81)	4(14.81)	0.902
		2(7.4)	0.311
Lung involvement according to HRCT			0.310
≤50%	73(67.59)	11(40.74)	
>50%	35(32.40)	16(59.25)	

The mean SPO2 in survived patients was 86.85±5.55% which was higher than that of non-survived (82.93±11.37%) with a significant difference. Additionally, the mean RR in the non-survived group was 34.07±9.47breaths/min compared with 23.27±9.28 breaths/min in survived patients with a significant difference (Table 7).

Table 7.

Association of vital signs with survival rate

Variables	Survived n(108)	Died n(22)	P-value
SPO_2 Mean±SD Range	86.85±5.55 60-99	82.93±11.37 60-90	**0.024**
RR, breaths/min Mean±SD Range	23.27±9.28 15-25	34.07±9.47 15-50	**0.018**
Pulse rate, beats/min Mean±SD Range	89.52±17.95 51-110	92.81±22.34 58-153	0.419
Temperature, ºC Mean±SD Range	37.13±1.03 36.1-40.5	37.51±1.05 36.1-40.5	0.084
SBP, mmHg Mean±SD Range	127.4±19.37 70-195	126.15±25.2 70-140	0.779
DBP, mmHg Mean±SD Range	75.56±12.6 50-110	76.15±14.66 50-110	0.835

At admission, the mean serum level of PCT and CRP in dead patients was 0.22±0.6 ng/ml and 164.0±105.59 mg/L, respectively compared with 0.07±0.08 ng/ml and 101.42±82.03 mg/L, respectively in survived group with highly significant differences (Table 8).

After 10 days of admission, the mean serum level of PCT and CRP in dead patients was 1.5±2.74 ng/ml and 70.9±57.87 mg/L, respectively compared with 0.13±0.23 ng/ml and 37.7±34.87 mg/L, respectively in survived patients with highly significant differences (Table 9).

Table 8.

Mean serum level of CRP and PCT in survived and non-survived patients at admission

Markers	Survived (n=108)	Died (n=27)	p-value
PCT, ng/ml Mean±SD Range	0.07±0.08 0.02-0.6	0.22±0.6 0.02-3.21	**0.007**
CRP, mg/L Mean±SD Range	101.42±82.03 7.0-320	164.0±105.59 37.2-380	**0.002**

Table 9.

Median serum level of CRP and PCT in survived and non-survived patients after 10 days of admission

Markers	Survived (n=108)	Died (n=27)	p-value
PCT, ng/ml Mean±SD Range	0.13±0.23 0.02-1.37	1.5±2.74 0.02-12.79	0.010
CRP, mg/L Mean±SD Range	37.7±34.87 1.32-184	70.9±57.87 7.8-295.08	**<0.01**

The receiver operating characteristic (ROC) curve was used to evaluate the sensitivity and specificity of CRP and PCT in predicting the survival in patients with COVID-19. For PCT, the area under the curve (AUC) was 0.683, 95%CI= 0.560-0.806, p =0.007. The sensitivity and specificity of the test at the cut-off value of PCT= 0.14 ng/ml were 75% and 61%, respectively. For CRP, the AUC was 0.747, 95%CI= 0.648-0.847, p =0.002. The sensitivity and specificity of the test at the cut-off value of CRP = 61.5 mg/L were 75% and 70%, respectively (Figure 2).

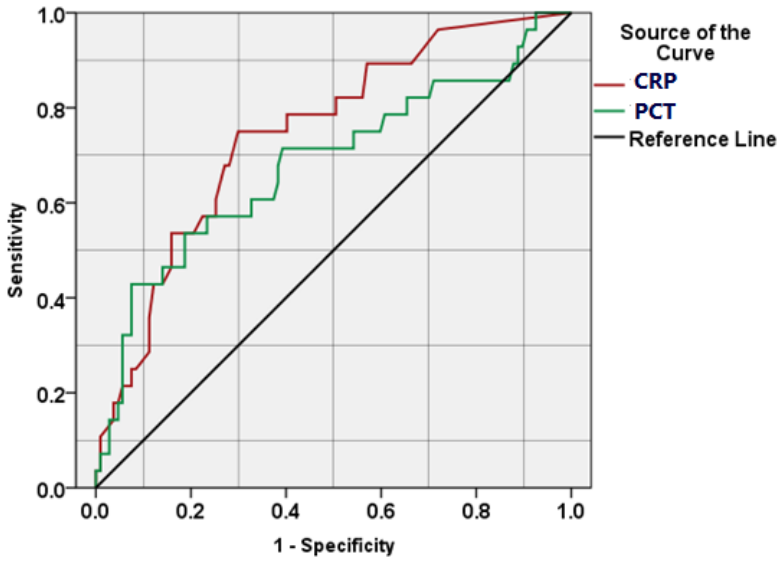

Figure 2.

Receiver operating characteristic curve for CRP and PCT at admission in predicting survival in patients with COVID-19.

At day 10 post admission, the AUC of PCT, AUC was 0.659, 95%CI= 0.551-0.767, p = 0.01. The sensitivity and specificity of the test at cut off value of PCT = 1.1 was 68% and 60%,

respectively. For CRP was 0.724, 95%CI= 0.620-0.827, p <0.001. The sensitivity and specificity of the test at cut off value of CRP = 34.79 mg/L was 63% and 60%, respectively as outlined in Figure 3.

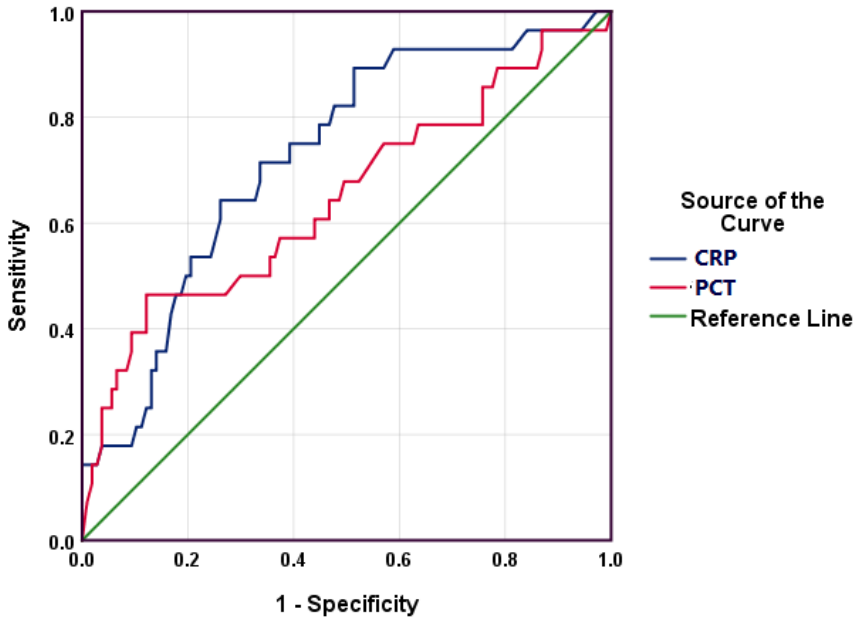

Figure 3.

Receiver operating characteristic curve for CRP and PCT at day 10 post-admission in predicting survival in patients with COVID-19.

Discussion

According to the results of the study, there was an elevation in PCT and CRP in patients with COVID-19 from day 1 to day 10 after admission. This result for PCT is in accordance with a Swiss study including 65 patients with COVID-19 admitted to ICU. There is a steady rise in PCT in those patients associated with the severity of the disease. The authors attributed this rise to secondary infection. Conversely, the other inflammatory markers were shown to have no any significant discriminatory associations [56]. This indicates the relative usefulness of serial PCT measurements in the identification of nosocomial bacterial infection and highlights its potential for guiding antimicrobial therapy in COVID-19 ICU patients.

On the other hand, two studies Zhang JJ et al and Liu F et al have shown that CRP levels correlate positively with disease severity and progression [57, 58].

In the present study, serum level of PCT and CRP was significantly higher in dead patients than survived patients whether at admission or 10 days post-admission.

In a similar study including 318 Serbian patients with COVID-19, Milenkovic et al. [59] investigated the predictive value of PCT in the prediction of mortality in those patients. At a

cut-off value of 0.56 ng/ml, PCT had a sensitivity and specificity of 81.1% and 76% respectively which is comparable to the present results.

In another study, Tong-Minh et al. [60] examined the association between PCT and the severity of COVID-19 in 332 Chinese patients. In the context of discrimination between survived and non-survived patients, PCT had a sensitivity and specificity of 57% and 87% at a cut-off value of 0.5 ng/ml.

A meta-analysis analyzed by Lippi G et al. [61] proved that an increase in PCT is associated with a five times higher risk of a more severe COVID-19 presentation (OR, 4.76; 95% CI, 2.74–8.29). Furthermore, another meta-analysis by Malik P et al. [62] which included over 10 thousand patients indicated the importance of elevated PCT values as a predictor of fatal disease outcomes. The same study showed that lymphopenia, thrombocytopenia, elevated D-dimer, and elevated CRP, are independent predictors of deadly disease outcomes.

SARS-CoV-2 can trigger an inflammatory cascade via the release of pro-inflammatory cytokines, such as IL-1β and IL-6, after activating Toll-like receptors which are also known to stimulate the release of PCT [63]. A study done by Wang D et al. [64] in china showed that elevated PCT in severe COVID-19 patients is co-infection with bacteria. Severe, critical, and dead COVID-19 patients were more likely to have a co-infection or multiple organ failure

Besides being a biomarker of severity, PCT is a mediator of sepsis and possibly COVID-19. Gautam S et al. [65] suggests severe respiratory viral infection-induced procalcitonin in the absence of bacterial pneumonia. It upregulates surface markers on neutrophils/lymphocytes and upregulates cytokines and reactive oxygen species (ROS). This positive feedback between procalcitonin and proinflammatory cytokines subsequently culminates in a severe systemic inflammatory response.

In a meta-analysis, Biswas et al. [66] showed that elevated serum CRP, procalcitonin (PCT), D-dimer, and serum ferritin levels were associated with an increased poor outcome that comprises mortality, severe COVID-19, ARDS, and the need for ICU care in patients with COVID-19. In another study by Kazemi E et al. [67] in iran, the severe COVID-19 patients were split up into discharge group and death event group and found a significant correlation between CRP and death event.

Likewise, Chen W et al. [68] in China demonstrated a progressive increase in the CRP level from mild, moderate, and severe pneumonia. It is now well established that pneumonia is the most common clinical feature of symptomatic SARS-CoV-2 infection. Also, the severe form of pneumonia resulting from excessive inflammation contributed to the loss of lives related to COVID-19. CRP is an indicator of systemic inflammation. Therefore, the level of CRP may clearly show not only the progression of mildly infected individuals but also dictate the recovery or adverse outcome of severe patients. A study in the United Kingdom strongly evidenced that the most accurate predictor of death was found to be IL-6, with CRP coming in second. Stringer D et al [69].

In the present study, the mortality rate of hospitalized patients with COVID-19 is 20%. This rate is relatively higher than that reported for in-hospital patients with COVID-19. Population-based studies done by Chen Y et al reported 5.3% in Hubei, China [70]. Souris M et al. [71] study shows 6.05% in the United States, 11.76% for Spain, 13.98% for Italy, 14.37% for the United Kingdom and 19.35% for France. Such discrepancies can be explained by the way the COVID-19 cases are confirmed and deaths registered. In most countries, only in-hospital deaths are recorded, while in countries like Mexico, in the absence of symptoms, tests are not used to exclude the infection [72]. The relatively higher rate in the present study may be explained by several factors mainly the older age of the patients and the prevalence of comorbidities and patient's symptoms range from moderate, severe to critical.

According to the present study, older age patients are more prone to mortality than younger age patients. Age may be considered the most risky demographic factor which has been confirmed as a predictor of mortality in different studies worldwide. In a large Spanish cohort done by Borobia AM et al involving 2226 patients, the mortality rate for younger patients was 0.5 % for those below 40 years, 1.5 % for those 40–49 years, and 3.8 % for those 50–59 years [73].

The condition of geriatric patients also increases the likelihood of a cytokine storm when exposed to COVID-19 because geriatrics has an immunosenescence condition (decreased immunity in old age) [74]. The presence of immunosenescence in the elderly causes susceptibility to respiratory tract infections. This can occur due to reduced mucosal barrier, mucociliary clearance, immune response, and the presence of respiratory inflammation against pathogenic microorganisms [75].

In the present study T2DM, malignancy, and heart failure were significantly associated with increased mortality rate. This is in accordance with almost all previous studies.

Guan et al. [76] analyzed data from 575 hospitals in China. The endpoint of the study consisted of admission to ICU, invasive ventilation, or death. Among laboratory-confirmed cases of COVID-19, patients with any comorbidity yielded poorer clinical outcomes than those without. Diabetes, hypertension, and malignancy were risk factors for reaching these end-points. The hazard ratio was 1.79 among patients with at least single comorbidity and 2.59 among patients with two or more comorbidities.

Two systematic reviews and meta-analysis Ssentongo P et al and Zhou Y et al. CVD, hypertension, diabetes, chronic kidney disease, and cancer were identified as risk factors for COVID-19 mortality [77, 78]. Similar results were reported from a study in the United Kingdom done by Docherty AB et al. [79] based on hospitalized COVID-19 patients in the first wave of the pandemic.

There are at least two possible explanations for the increased prevalence of diabetes among fatal cases. Immune dysfunction occurs in diabetic patients as innate immunity is often compromised. There may be exaggerated pro-inflammatory cytokine expression in diabetes,

which could contribute to the cytokine storm that is seen in severe COVID-19 cases [80]. It has been reported that ACE2 may be downregulated in diabetics [81]. While this may seem beneficial as there would be fewer receptors available for SARS-CoV-2 to enter cells, ACE2 has been shown to be anti-inflammatory, and thus possibly even protective in other types of pneumonia of infectious etiologies [82]. Therefore, the low expression of ACE2 in diabetic patients may contribute to fatal disease by contributing to uncontrolled inflammation in the lungs.

In our study cancer patients with COVID-19 infection have a poor prognosis, this in accordance with Zhang H et al in which COVID-19 patients with cancer seem to have a higher proportion of severe cases and poorer prognosis [83].

Same result by Ma J et al. [84] the proportion of severe/critical COVID-19 patients with cancer is high which is also significantly higher than that of the general population. They, therefore, encouraged clinicians to treat patients with cancer as an extremely vulnerable population. Those studies might also raise issues as to whether it is futile to admit patients with cancer and COVID-19 to the ICU [85]. On the other hand, Spezzani V et al. [86] suggested that there was no evidence of elevated mortality rates among infected patients with cancer. An interesting theory even suggested that immunocompromised patients, such as patients with cancer, may dampen the so-called “cytokine storm” because of downregulated immune response and thus have comparable or even better clinical outcomes. The results of our meta-analysis might help to reveal the true effect of cancer on mortality and the need for ICU admission.

Clinically, reduced SPO2 and increased respiratory rate were significantly associated with the increased mortality rate in the present study.

Chatterjee et al. [87] showed that SPO2 <92% or a respiratory rate >22 breaths per minute were associated with elevated mortality in hospitalized COVID-19 patients. In the US study, Petrilli et al. [88] noticed that hypoxic patients (out-of-hospital SpO2 < 88% vs 92%) were twice as likely to die (HR, 2.00; 95% CI, 1.61–2.48; P < 0.001). In a Chinese study, Xie J et al. [89] the SpO2 percentage was inversely related to survival (out-of-hospital SpO2 per 1-unit increase; HR, 0.93, 95% CI, 0.91–0.95; P < 0.001).

Conclusion

This study concluded that serum level of both PCT and CRP increases during the course of COVID-19 from admission to day 10 post-admission. Serum levels of PCT and CRP at admission and day 10 post-admission are indicators of severe inflammatory response and could increase the risk of mortality. Demographically, advanced age and the comorbidities like diabetes, hypertension, and malignancy are predictors for the development of severe infection

in COVID-19 with a worse prognosis. Clinically, low SPO_2 and increase respiratory rate are associated with increased mortality in those patients.

Recommendation

The authors recommend that high serum levels of PCT and CRP at admission or 10 days post-admission could be used as additional markers to predict worse prognosis in those patients that may be due to secondary bacterial infection. Older age patients and those with comorbidities, especially DM, hypertension, and cancer, the presence of high respiratory rate, and low SPO2 should direct clinicians to effectively prioritize resources for patients at high risk of mortality.

Human and animal rights

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

Consent for publication

We obtained the written informed consent from each subject or subject's parent.

Conflict of interest

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

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