

**PROGNOSTIC VALUE OF THE LABORATORY PARAMETERS D-DIMER AND
PROCALCITONIN IN COVID 19 PATIENTS AT TISHREEN UNIVERSITY HOSPITAL**Riham Khaddour^{1*}, Faisal Radwan¹ and Malek Hejazie²¹Department of Laboratory Medicine, Professor, Tishreen University, Faculty of Medicine, Lattakia, Syria.²Department of Pulmonary Diseases, Professor, Tishreen University, Faculty of Medicine, Lattakia, Syria.***Corresponding Author: Riham Khaddour**

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ABSTRACT

Background: Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has triggered a global health crisis that has affected populations and spread worldwide. It is clear whether outcome is modulated by serum levels of D-dimer and PCT, in which elevated levels of them are associated with poor outcome. **Aim:** The purpose of this study was to evaluate the role of D. dimer and PCT as potential predictors for COVID-19 induced fatal clinical complications in hospitalized patients. **Materials and Methods:** This was an Analytic Cohort study (Retrospective) involved 601 patients with confirmed diagnosis of COVID-19 admitted to quarantine unit, Tishreen University Hospital, Latakia. Patients were divided into two groups according to the levels of PCT and D-dimer, and final outcome was compared between groups. **Results:** Out of 601 patients, 359 were males and 242 were females, with mean age of the patients 63.08±14.2. D-dimer levels > 985 mg/L were detected in 342 cases, and PCT levels > 0.54 ng/ml in 43 cases, without the presence of significant differences between groups regarding of age and gender (p>0.05). Elevated levels of D-dimer were associated with an independent risk for mortality (RR: 2.1[1.3-4.2], p=0.001), need for mechanical ventilation (RR: 3.8[2.4-11.3], p=0.0001), admission in intensive care unit ICU (RR : 1.9[1.2-8.4], p=0.02), and prolonged duration of hospitalization (RR: 3.1[2.2-9.9], p=0.0001). In addition, elevated levels of PCT were associated with an independent risk for mortality (RR: 4.1[1.1-12.5], p=0.0001), need for mechanical ventilation (RR: 3.02[1.4-9.8], p=.0001), admission in intensive care unit ICU (RR : 2.2[0.9-7.2], p:0.004), and longer duration of hospitalization (RR: 3.8[1.9-11.3], p=0.0001). **Conclusion:** The current study demonstrated poor results of elevated levels of PCT and D-dimer on final outcome regarding morbidity and mortality in COVID-19 patients especially PCT levels.

KEYWORDS: COVID-19, PCT, D-dimer, outcome.**INTRODUCTION**

Coronaviruses include a wide group of viruses that have led to the development of respiratory infections with varying degrees of severity. Three types of these “beta” viruses caused numerous pandemics over the past two decades: the SARS virus and the MERS virus. In addition, SARS - CoV-2, which led to the COVID-19 pandemic at the end of 2019.^[1, 2]

This disease was first described in the city of Wuhan in China at the end of December 2019, and it spread globally within less than 3 months, with it being declared a global epidemic on March 11, 2020 by the World Health Organization (WHO). The original SARS -COV-2 presence has been identified on seven continents and approximately 222 countries, with the number of confirmed cases reaching 163,788,738 with a mortality rate of 2.1% as of March 24, 2020.^[3]

The Khaddour1manifestations of these diseases varied from the asymptomatic form or mild respiratory illness

to respiratory failure and the development of a life-threatening multi organ syndrome. There are many risk factors that predispose to the occurrence of the severe form and mortality, including advanced age, obesity, and accompanying diseases. In addition, patients with severe forms of the disease usually have a decreased lymphocytes count and an increase in inflammatory markers, procalcitonin, and D -dimer.^[4]

Procalcitonin (PCT) is a glycoprotein precursor of calcitonin without hormonal effects. Its levels are undeterminable in normal cases and increase in bacterial infections in order to modulate the host immune response and vascular activity in response to bacterial infection. In addition, PCT isn't induced in viral infections due to TNF- α inhibition by Interferon gamma.^[5]

D-Dimer represents a complex protein molecule that is formed during cross-linked fibrin breakdown mediated by Plasmin, which plays a role in fibrinolytic conditions, and therefore its assay may serve as a direct indicator of

these events and an indirect indicator of thrombotic activity.^[6]

Many studies have been conducted to identify rapid and sensitive methods to detect patients at high risk of complications, and various studies showed that elevated serum levels of PCT and D-dimer is associated with severe sepsis and with the development of significant morbidity and mortality in patients with COVID-19. Therefore, the aim of this research was to measure PCT and D-dimer levels in COVID-19 patients those admitted to the isolation department at Tishreen University Hospital in Latakia.

PATIENTS AND METHODS

This is an Analytic Cohort study (Retrospective) of a group of patients who have been admitted to the quarantine ward at Tishreen University Hospital in Latakia during one year period (2020 - 2021). The inclusion criteria were: patients older than 20 years, males or females, with a positive PCR test. Patients with incomplete data were excluded.

Data about the demographic and personal characteristics of the patients, as well as accompanying diseases, and laboratory findings upon admission were collected and recorded within the information collection form. A plain chest radiograph or chest Computed Tomography (CT) was performed depending on the case. Performed Laboratory tests included: complete blood count with differential, C-reactive protein (CRP) levels, and serum Lactate Dehydrogenase activity (LDH). Procalcitonin Assay was performed using venous blood samples collected in tubes without anti-coagulant to obtain serum. Patients who met Inclusion criteria were classified according to cut off value for PCT on admission 0.54 ng/ml to.

COVID19 patients with low PCT values (558 cases) and those with values higher than the upper limit of the normal range (43 cases).

D-dimer test was performed using 3.2% sodium citrate tubes with patients classified according to the cut off for D-dimer on admission 985 mg/L to.

COVID19 patients with low D-dimer values (259 cases) and the other group with D-dimer values above the cutoff

point (342 cases). The clinical course of the disease was followed in these patients in terms of duration of hospitalization, admission to the intensive care unit, need to use mechanical ventilation, and the resulting mortality rate.

Statistical Methods

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) program (version 20, IBM Corporation). A probability value of less than 0.05 (P Value<0.05) was considered statistically significant. Descriptive statistics: for categorical variables: frequency, percentages, and graphs were relied upon.

For continuous variables: measures of central tendency (Mean, standard Deviation, Range) were used.

Inferential statistics: All variables were tested according to Univariate regression with the exclusion of every variable that does not meet the condition of remaining in the study (not statistically significant). The Independent samples Student T test was used to study the Means differences between two independent groups, the chi-square test was used or (Fisher exact) to study the relationship between qualitative variables, and then variables with statistical value were entered into the logistic regression equation and the odds ratio (OR) was determined to study the risk associated with high levels of D-dimer and PCT on Prognosis within the hospital. The results were considered statistically significant with p-value < 5%.

RESULTS AND DISCUSSION

Results

Demographic characteristics of study population:

Patients' ages ranged between 20-95 year. The average age was 63.08 ±14.2 year. The number of males was 359 cases (59.7%) and females 242 cases (40.3%) with Sex Ratio (M: F) = 1.5:1.

High blood pressure was the most frequently observed Accompanying illness in 295 cases (49.1%), followed by Diabetes Mellitus in 194 cases (32.3%), cardiovascular disease in 130 cases (21.6%), and COPD in 17 cases (2.8%).

Table (1): Distribution of 601 patients according to demographic variables.

variable	number	Percentage
Sex		
Males	359	59.7%
Females	242	40.3%
Accompanying diseases		
High blood pressure	295	49.1%
Diabetes Mellitus	194	32.3%
Cardiovascular diseases	130	21.6%
COPD	17	2.8%

Comparison of demographic characteristics of study population according to D-dimer values.

The number of males in the group of patients with a high D-dimer was 204 cases (59.6%) and females were 138 cases (40.4%), compared to 155 cases (59.8%) and 104 cases (40.2%), respectively, in patients with a D-dimer less than 985. Without significant differences, $p=0.9$. The mean age was higher with higher D-dimer values

64.25 \pm 13.5 vs. 62.52 \pm 14.9 However, there were no statistically significant differences, $p=0.07$. There is statistically significant differences between the two groups of patients with D-dimer higher than 985 versus values lower than that with regard to high blood pressure: 55.8% versus 40.1%, $p=0.002$, and diabetes: 38.3% versus 24.3%, $p=0.01$.

Table (2) Demographic distribution differences between the two groups of patients According to values of D-Dimer.

Demographic variables	D-Dimer>985 mg/L	D-Dimer<985 mg/L	P-value
Sex			
Males	204(59.6%)	155(59.8%)	0.9
Females	138(40.4%)	104(40.2%)	
Age	64.25 \pm 13.5	62.52 \pm 14.9	0.07
Accompanying diseases			
High blood pressure	191(55.8%)	104(40.1%)	0.002
Cardiovascular diseases	80(23.4%)	50(19.3%)	0.2
Diabetes	131(38.3%)	63(24.3%)	0.01
COPD	13(3.8%)	4(1.5%)	0.09

Comparison of laboratory parameters for the study patient sample according to D-dimer values

It was observed that there were statistically significant differences between the two groups of patients with D-dimer higher than 985 mg/L versus values lower than that with regard to the following measures: HGB g/dl (10.39 \pm 2.1 vs. 11.93 \pm 1.8, $P=0.04$), WBC

(11590.71 \pm 6141.6 vs. 10034.01 \pm 5006.2, $P=0.001$), Lymphocytes count (844.72 \pm 531.8 vs. 942.78 \pm 545.4, $P=0.03$), CRP mg/dl (125.89 \pm 67.1 vs 96.68 \pm 71.2, $p=0.0001$). LDH IU/L (788.32 \pm 419.8 vs 513.26 \pm 328.4, $p=0.0001$) and PCT ng/ml (0.3 \pm 0.4 vs 0.16 \pm 0.1, $p=0.0001$).

Table (3) Comparison of Laboratory parameters between the two groups of patients According to D-dimer values.

Laboratory parameters	D-Dimer>985 mg/l	D-Dimer<985 mg/l	P-value
HGB g/dl	10.39 \pm 2.1	11.93 \pm 1.8	0.04
WBC	11590.71 \pm 6141.6	10034.01 \pm 5006.2	0.001
LYM	844.72 \pm 531.8	942.78 \pm 545.4	0.03
CRP mg/dl	125.89 \pm 67.1	96.68 \pm 71.2	0.0001
LDH IU/L	788.32 \pm 419.8	513.26 \pm 328.4	0.0001
PCT ng/ml	0.30 \pm 0.4	0.16 \pm 0.1	0.0001

Comparison of the outcome of the study patient sample according to D-dimer values

The need for ventilation was present in 11 cases (7.3%) in patients with a D-Dimer > 985 mg/L, compared to 4 cases in patients with a D-Dimer < 985 mg/L, with significant differences, $p=0.002$. There was a need for admission to intensive care unit in 67 cases (44.4%) in patients with D-Dimer > 985 mg/L compared to 64 cases (34%) in patients with D-Dimer < 985 mg/L, with significant differences, $p=0.04$. The duration of hospitalization ranged between 2-25 days, with an

average duration of 7.81 \pm 4.4 day in the group of patients with a D-Dimer > 985mg/L, while in the group of patients with a D-Dimer < 985mg/L, the duration of hospitalization ranged from 2 to 20 days, with an average duration of 4.69 \pm 3.8 day, with Significant differences, $p=0.002$. The mortality rate was 55.6% (190 cases) in the group of patients with D-Dimer >985 mg/L, compared to 71 cases (27.4%) in patients in the second group, with significant differences between the two groups, $p=0.0001$.

Table 4: Final outcome between the two groups of patients According to values of D-Dimer.

variable	D-Dimer>985	D-Dimer<985	P-value
Automated ventilation			
present	11(7.3%)	4(2.1%)	0.02
not available	140(92.7%)	184(97.9%)	
Need for intensive care			
present	67(44.4%)	64 (34%)	0.04

not available	84 (55.6%)	124 (66%)	
Hospitalization time (day)	7.81±4.4 (2-25)	4.69±3.8 (2-20)	0.002
Deaths	190(55.6%)	71(27.4%)	0.0001

Multivariate analysis of D-Dimer in COVID-19 patients

Table 5 shows that high D-Dimer is a risk factor for: death where the risk was about 2.1 times greater if present OR: 2.1[1.3-4.2], p=0.001, longer hospitalization

duration about 3.1 times OR:3.1[2.2-9.9], the need to use mechanical ventilation was 3.8 times greater OR:3.8[2.4-11.3], and the need for admission to intensive care was approximately 1.9 times greater OR:1.9 [1.2-8.4]

Table 5: Multivariate analysis of D-Dimer in Covid -19 patients.

Variables	RR a [CI95%]	p-value
Death	2.1[1.3-4.2]	0.001
Need for mechanical ventilation	3.8[2.4-11.3]	0.0001
Intensive care	1.9[1.2-8.4]	0.02
Duration of hospitalization	3.1[2.2-9.9]	0.0001

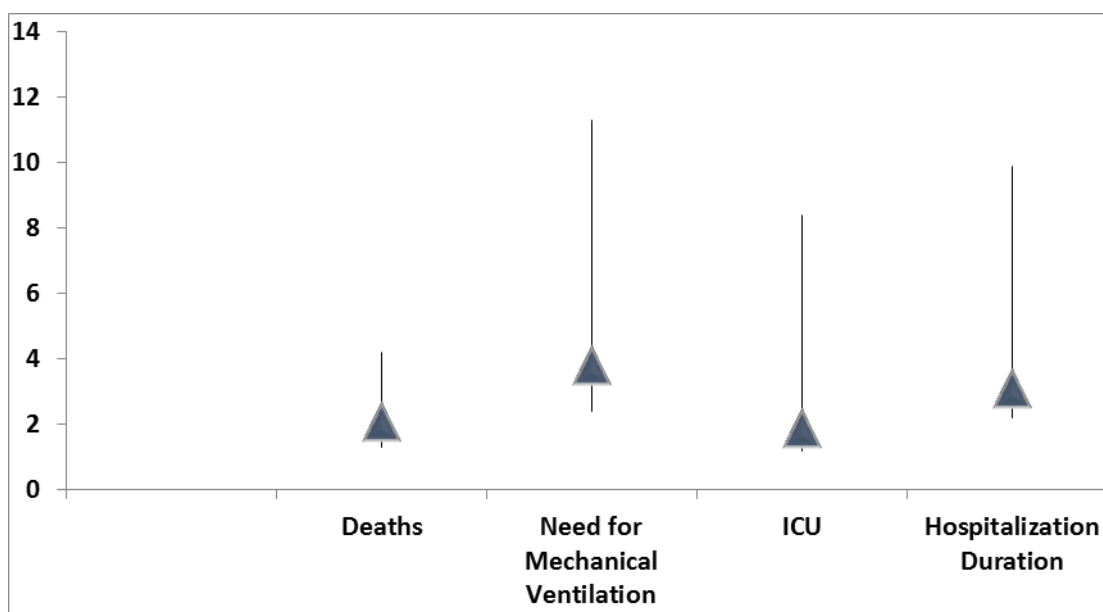


Figure (1) Multivariate analysis of D-Dimer values In COVID- 19 patients.

Comparison of demographic characteristics of the study patient sample according to PCT values

The number of males in the group of patients with a high PCT was 28 cases (65.1%) and females 15 cases (34.9%), compared to 331 cases (59.3%) and 227 cases (40.7%) respectively in patients with a PCT of less than 0.54, without any significant differences, p= 0.4. The average age was 63.20±13.9 years in patients with high

PCT values, compared to 63.07±14.2 in the second group, but without significant differences, p= 0.9. No statistically significant differences were observed between the two groups of patients with PCT higher than 0.54 versus values lower than that with regard to hypertension (p: 0.3), cardiovascular diseases (p: 0.9), diabetes (p: 0.7) and COPD (p: 0.2).

Table (6): Differences in demographic distribution between the two groups of patients According to PCT values.

Demographic variables	PCT>0.54 ng/ml	PCT<0.54 ng/ml	P-value
Sex			
Males	28(65.1%)	331(59.3%)	0.4
Females	15(34.9%)	227(40.7%)	
the age	63.20±13.9	63.07±14.2	0.9
Accompanying diseases			
High blood pressure	24(55.8%)	271(48.6%)	0.3
Cardiovascular diseases	9(20.9%)	121(21.7%)	0.9
Diabetes	13(30.2%)	181(32.4%)	0.7
COPD	0(0%)	17(3%)	0.2

Comparison of laboratory parameters of the study patient sample according to PCT values

It was observed that there were statistically significant differences between the two groups of PCT patients with values higher than 0.54 versus values lower than that with regard to the following measures: HGB (10.03±2.3

vs. 11.72±1.9, p:0.03), WBC (13568.3±6557.3 vs. 10715.76±5613.9, p:0.002), LYM (825.58±616.09 vs. 900.54±532.5, p:0.04), CRP (166.88±64.6 vs. 109.18±69.1, p:0.0001), LDH (899.59±378.9 vs. 652.07±403.3, p:0.0001), D-Dimer (3162.44±2858.7 vs. 812.18±2110.3, p:0.0001).

Table 7: Laboratory parameters between the two groups of patients According to PCT values.

Laboratory parameters	PCT>0.54	PCT<0.54	P-value
HGB	10.03±2.3	11.72±1.9	0.03
WBC	13568.3±6557.3	10715.76±5613.9	0.002
LYM	825.58±616.09	900.54±532.5	0.04
CRP	166.88±64.6	109.18±69.1	0.0001
LDH	899.59±378.9	652.07±403.3	0.0001
D-Dimer	3162.44±2858.7	812.18±2110.3	0.0001

Comparison of the final outcome of the study patient sample according to PCT values

The need for ventilation was present in one case (11.1%) in patients with PCT >0.54 ng/ml versus 13. Cases (3.9%) in patients with PCT < 0.54 ng/ml and with significant differences, p=0.02. There was a need for admission to intensive care in 5 Cases (55.6%) in patients with PCT >0.54 ng/ml compared to 125 cases (37.9%) in patients with PCT <0.54 ng/ml, with significant differences, p=0.01. The duration of

hospitalization ranged from 2 to 25 days, with a mean duration of 8.12±5.7 day in the group of patients with PCT >0.54 ng/ml, while in the group of patients with PCT <0.54 ng/ml, the duration of hospitalization ranged from 2 to 17 days, with an average duration of 6.22±4.06 days, with significant differences, p=0.0001. The mortality rate was 34 cases (79.1%) in the group of patients with PCT >0.54 ng/ml vs. 227 Cases (40.7%) among patients in the second group, with significant differences between the two groups, p=0.0001.

Table 8: Final outcome between the two groups of patients According to PCT values.

variable	PCT>0.54 ng/ml	PCT<0.54 ng/ml	P-value
<u>Automated ventilation</u>			
present	1(11.1%)	13(3.9%)	0.02
not available	8(88.9%)	317(96.1%)	
<u>The need for intensive care</u>			
present	5(55.6%)	125(37.9%)	0.01
not available	4(44.4%)	205(62.1%)	
<u>Hospitalization time (day)</u>	8.12±5.7 (2-25)	6.22±4.06 (2-17)	0.0001
<u>Deaths</u>	34(79.1%)	227(40.7%)	0.0001

Multivariate analysis of PCT in COVID-19 patients

Table (9) shows that high PCT levels is a risk factor for: death, where the risk was about 4 times greater if present OR:4.1 [1.1-12.5], longer hospitalization time about 3.8

times OR:3.8 [1.9-11.3], and the need to use mechanical ventilation at a rate of 3.02 times OR: 3.02[1.4-9.8], and the need for admission to intensive care is approximately 2.2 times greater OR: 2.2 [0.9-7.2].

Table 9: Multivariate analysis PCT values In COVID- 19 patients.

Variables	RR a [CI 95%]	p-value
Deaths	4.1[1.1-12.5]	0.0001
Need for mechanical ventilation	3.02[1.4-9.8]	0.0001
Intensive care	2.2[0.9-7.2]	0.004
Duration of hospitalization	3.8[1.9-11.3]	0.0001

This has been represented in Figure 2.

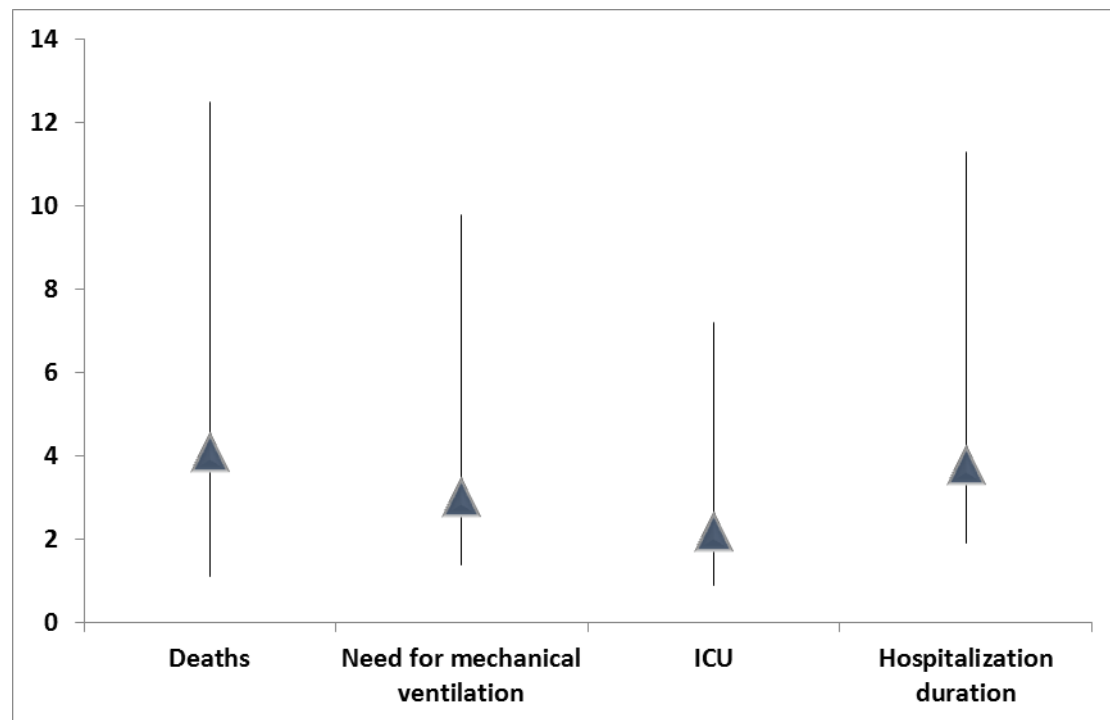


Figure (2) Multivariate analysis of PCT values In COVID- 19 patients.

DISCUSSION

SARS COV-2 virus has caused a global pandemic with very high morbidity and mortality rates. D-Dimer along with PCT are among the most used tests in monitoring COVID-19 patients. About two-thirds of patients are males. This may be due to the immunosuppressive effects of testosterone compared to the enhancing effect of estrogen in females, and the greater exposure to environmental toxins by males. High blood pressure is the most frequent comorbidity, and this may be due to the fact that a significant proportion of patients are of advanced age, where there is a lack of resistance to infections.

Elevated D-dimer levels were detected in 342 cases, without significant differences between the two groups with regard to age, sex, cardiovascular diseases, and COPD. Oxygen saturation values were statistically significantly lower with higher D-dimer levels.

It was noted that there were statistically significant differences between the two groups (D-Dimer >985 mg/l, D-Dimer < 985 mg/l) with regard to laboratory parameters ($p < 0.05$), with significant differences between the two groups with regard to mechanical ventilation ($p = 0.02$), admission to the intensive care unit ($p = 0.04$), and duration of hospitalization ($p = 0.04$), and the mortality rate ($p = 0.0001$), which were all higher with higher D-dimer values. Elevated D-dimer was an independent risk factor for death and poor final outcome for patients. The above findings may be explained by hyperfibrinolysis and increased inflammatory status induced by SARS-COV-2 infection, hypoxia that leads to activation of prothrombotic pathways, and a higher

frequency of the incidence of the disease in the elderly with comorbidities that predispose to thrombosis.

Elevated PCT Levels were found in 43 cases, without significant differences between the two groups (PCT < 0.54 ng/ml and PCT > 0.54 ng/ml) with regard to age, sex, and comorbidities. It was noted that there were statistically significant differences between the two groups with regard to laboratory parameters ($p < 0.05$), with significant differences between the two groups with regard to mechanical ventilation ($p = 0.02$), admission to the intensive care unit ($p = 0.01$), and duration of hospitalization ($p = 0.0001$), and the mortality rate ($p = 0.0001$), which were all higher with higher PCT values. High PCT was an independent risk factor for death and poor final outcome for patients.

The previous findings can be explained as follows: SARS -COV- 2 infection causes a systemic and local inflammatory response Mediated With proinflammatory cytokines, IL-1 stimulates the secretion of TNF- α and IL-6 and other cytokines in a proinflammatory complex that leads to a cytokine storm with pulmonary and systemic injury and the release of PCT associated with the proinflammatory cytokines.

Huang et al(2020)^[7] have found in an analytic study of 25 researches that A PCT elevation of more than 0.5 ng/ml has a sensitivity of 88% and specificity of 68% in predicting a poor outcome of the disease. And high D-dimer levels were associated with poor final outcome (RR: 2.9) and mortality (RR: 4.1), and a D-dimer value greater than 0.5 mg/L has a sensitivity of 58% and a specificity of 69%. In predicting a bad outcome. And this was compatible with our results where elevated PCT and

D-Dimer levels were associated with poor outcome in COVID-19 patients.

Huang et al (2020)^[8] demonstrated in a study included 676 COVID-19 patients in China that D-Dimer level greater than 0.5mg/L was found in 83.2% of non-survival patients vs 44.9% in survival group, $p = 0.01$.

PCT more than 0.5 ng /ml (mortality 27.7% vs. survival 1.8%, $p = 0.001$).

After admission and during follow-up, D-dimer continued to rise in patients who developed death, with PCT stabilizing after admission.

D-dimer greater than 0.5 mg/l is a risk factor for death HR:4.39 with $p = 0.001$. And this contradicts what our study found that high PCT level was a greater risk factor for mortality compared with D-dimer.

Zhou et al(2020)^[9] found in a study on 48 patients that PCT values were higher in very severe cases of the disease compared to severe cases (0.21 vs. 0.05 with $p = 0.001$) PCT was a risk factor for severe disease with an OR: 4.5 with $p = 0.03$. And this is consistent with our study results where high PCT levels studies were associated with poor final for patients.

On a study conducted by Yao et al(2020) China^[10] it was found that D-dimer values > 2.0 mg/L on admission were associated with an increased risk of mortality OR:10.7. D-dimer levels increase with increasing disease severity depending on the clinical and radiological classification. The mean D-dimer value in patients who died was higher compared to those who survived (6.2 vs. 1.02) with $P = 0.001$.

The cut-off point for D-dimer was 2.14 mg/L with higher values being predictive of mortality with a sensitivity of 88.2% and specificity of 71.3%. Compared with the current study, both studies agreed that increased D-dimer is associated with a poor final outcome for COVID-19 patients.

In summary: Elevated PCT and D-dimer levels were associated with an increased need for mechanical ventilation, admission to intensive care, increased mortality, and prolonged hospitalization. The value of D-dimer > 985 ng/ml has a predictive value for the occurrence of deaths and a poor final outcome. It is considered the value of PCT 0.54 ng/ ml has a greater predictive value for mortality compared to D-dimer. So it is possible to adopt both D-dimer And PCT levels upon admission as a warning indicator for COVID - 19 patients to identify high-risk patients based on how much they are elevated.

REFERENCES

1. de Wit E, Munster V, Falzarano D. SARS and MERS: Recent insights into emerging coronavirus. *Nat Rev Microbiol*, 2016; 14: 523-34.
2. Petrosillo N, Viceconte G, Ergonul O. COVID-19, SARS and MERS: Are they closely related? *Clin Microbiol Infect*, 2020; 26: 729-34.
3. Perlman S. Another decades, another coronavirus. *N Engl J Med*, 2020; 382: 760-762.
4. Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 2020; 395: 497.
5. Davies J. Procalcitonin. *J Clin Pathol*, 2015; 68: 675-9.
6. Thachil J, Lippi G, Favaloro E. D-dimer testing: laboratory aspects and current issues. *Methods Mol Biol*, 2017; 1646: 91–104.
7. Huang I, Pranata R, Lim M. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease, 2019: a meta-analysis. *Ther Adv Respir Dis*, 2020; 14: 1–14.
8. Huang Y, Lyu X, Li D. A cohort study of 676 patients indicates Ddimer is a critical risk factor for the mortality of COVID- 19. *PLoS ONE* 15(11): e0242045. <https://doi.org/10.1371/journal.pone.0242045>.
9. Zhou B, She J, Wang Y. Utility of Ferritin, Procalcitonin, and C-reactive Protein in Severe Patients with 2019 Novel Coronavirus Disease. Doi: 10.21203/rs.3.rs-18079/v1.
10. Yao Y, Cao J, Wang Q. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. *Journal of Intensive Care*, 2020; 8: 2020.