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Research Article

Value of D-dimer, P-selectin, and fibrinogen as biomarkers for patients with Covid-19

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Abstract

Background: Due to coronavirus's simple means of transmission, COVID-19 spread like wildfire. The use of biomarkers in emergency departments for corona virus infection screening and early diagnosis is gaining more attention. **Aim and objectives:** This study aimed to evaluate D-dimer, fibrinogen and p-selectin levels in hospitalized Covid-19 patients and its correlations with other routine investigations for predication of their prognosis. **Subjects and methods:** On 40 covid-19 patients, levels of D-dimer, fibrinogen, and soluble P-selectin in both ICU and non-ICU patients were measured and correlations with other routine investigations were done. **Results:** According to D-dimer, p-selectin, and fibrinogen among the groups under study, there was a statistical significance increase in D-dimer and p- selectin in both ICU ($p<0.001$, 0.0001) and non- ICU ($p=0.014$, 0.0001) when compared with control. But, fibrinogen was decrease in non-ICU when compared with control group ($p=0.0001$) and then start to increase in ICU patients when compared with non ICU patients ($p=0.029$). **Conclusions:** All physicians are extremely concerned about the worldwide emergency of COVID-19 disease. Therefore, readily available biomarkers including D-dimer, fibrinogen, and p-selectin are useful for determining and suspecting the fate of COVID-19, particularly in patients who are hospitalised.

Keywords: COVID; non-ICU; ICU; D-dimer; P-selectin.; fibrinogen.

Introduction

Acute respiratory distress syndrome, sepsis, and multi-organ failure are all possible clinical symptoms of the coronavirus disease 2019 (COVID-19), an infectious disease brought on by the coronavirus-2 (SARS-CoV-2) that causes a severe acute respiratory syndrome (ARDS) [(1)]**.** The global effects of this epidemic have been severe, and our knowledge of this illness is constantly advancing [(2)]. Recent variants, such as the Delta and Omicron variants, have resulted in a large increase in cases. It should be remembered that three days before symptoms develop, viral shedding might begin, and that more than 50% of viral transmission occurs in asymptomatic individuals **(3)**.Clinical risk factors for more life-threating disease form include gender, advanced age, and concomitant conditions like diabetes mellitus and hypertension [(4)]**.** In severe cases of covid-19 infection, Feng and his colleagues postulated that a cytokine storm—an overactive immune-logical response—is triggered. A cytokine storm is a potentially lethal immune disorder characterized by the increased level of activation of immune cells and excessive production of massive inflammatory cytokines and chemical mediators **(5)**. It is thought to be the main cause of disease severity and death in COVID-19 patients and is linked to elevated levels of circulating cytokines, severe lympho-penia, thrombosis, and massive mononuclear cell infiltration in multiple organs **(6)**.

Corona virus infection has been connected to early laboratory changes ever since reports first began**(7)**; Additionally, COVID-19 problems and prognosis have been connected to coagulation disorders**.** The use of biomarkers in the early detection of SARS-CoV-2 infection at

emergency departments is gaining more attention [8].Biomarkers, mostly blood chemistry markers show the activation of coagulation and fibrinolysis processes by the synthesis and lysis of cross-linked fibrin's D-dimer among Covid-19 patients [9]. According to reports, Covid-19 was connected to haemostatic problems, and those who didn't survive had dramatically higher D-dimer levels [10].

As the last stage of a triggered coagulation activity, fibrinogen, one of the acute phase proteins, is implicated in fibrin production and is produced by liver in significant amounts in response to IL-1 and IL-6. According to the worldwide organisation for thrombosis and haemostasis, fibrinogen has already been shown to be valuable and has been selected as one of the scoring parameters in DIC diagnosis. Leukocyte and platelet adhesion to inflammatory and damaged sites is mediated by P-selectin which on the other hand, increased its expression on damaged endothelial cells and activated platelets promotes a pro-thrombotic environment that results in immunothrombosis and thrombo-inflammation [11].

In this study, hospitalised Covid-19 patients' levels of D-dimer, fibrinogen, and p-selectin will be assessed.

Subjects and methods

At clinical pathology department at Minia University Hospitals conducted this prospective study on 60 people between January 2021 and February 2022, including 20 seemingly healthy subjects and 40 hospitalised patients with COVID-19 symptoms. This study received approval from the hospital ethics committee, and each patient provided written consent. The sample size was calculated by G power version 3.1.9.2 and it was equal 51 subjects[12]. The sample was collected= 60 subjects divided into three groups (20 subjects in each group).

The study's participants were divided into: Group-I that further subdivided into Ia: included 20 patients with mild-moderate symptoms who were not admitted to the chest ICU and Ib: it included 20 patients with severe COVID-19 symptoms who were admitted to the chest ICU for 9 to 19 days. Group II consisted of 20 apparently healthy people as a control group. All patients had PCR-positive RNA for the COVID-19 virus, and those having a history of thrombosis, sepsis, a propensity for bleeding, or autoimmune disease were not included in the study.

Every participant in the study will subjected to:

1) History taking for oxygen saturation, the existence of cough, fever, dyspnoea, sore throat, loss of taste and smell, thrombosis, the presence of sepsis, autoimmune illness, and co-morbidities. 2) Routine laboratory investigations included: Complete blood count (C.B.C), Erythrocyte sedimentation rate, C – reactive protein, D-dimer and serum ferritin. 3) Specific laboratory investigations included: P-selectin by ELISA (ELK Biotechnology, China) and Fibrinogen level using fully automated (stago, sta compact max, France).

Statistical Analysis:

The IBM SPSS statistical package software, version 26.0, was used to analyse the data (IBM; Armonk, New York, USA). By use of the Kolmogorov-Smirnov test, the data's normality was evaluated. Non-parametric quantitative data were expressed as median (IQR), whereas qualitative data were expressed as both number and percentage. For non-parametric quantitative data between the three groups, the Kruskal Wallis test wasconducted, followed by the Mann Whitney test for each pair of groups. Chisquare and Fisher's exact tests were used to compare categorical variables. For non-parametric data, Spearman's rank correlation was performed. The p-value for results that were deemed significant was less than 0.05. For determining sensitivity and specificity of focused and routine studies to make predictions, a receiver operating characteristic curve (ROC) was created.

Results

The demographic data among studied groups represented in Table (1). We found that ICU patients were older than non ICU and control groups. Additionally, the percentage of diabetes mellitus (65%), hypertension (60%) and smoking (40%) were statistical significance increase in ICU when compared with non ICU patients and control group (p=0.005, 0.002, <0.001 respectively).

Table (1): Demographic data of studied groups:

		Group I		Group II	p value	ICU vs non-ICU	ICU vs Control	Non-ICU vs Control
		Non-ICU N= 20	ICU N= 20	Control N= 20				
Age (years)	**IQR** **Mean ± SD** **Median**	(38 – 56.8) 46.1 ± 12.7 46	(48.3 – 62.8) 55.2 ± 12.5 58	(26.3 - 42) 34.9 ± 13.8 30	**0.0001***	0.166	**0.0001***	0.07
Gender: **Males** **Females**	**N %**	12 (60%) 8 (40%)	12 (60%) 8 (40%)	15 (75%) 5 (25%)	0.571	-	-	-
DM: **Yes** **No**	**N %**	8 (40%) 12 (60%)	13 (65%) 7 (35%)	3 (15%) 17 (85%)	**0.005***	0.113	**<0.001***	0.077
Hypertension **Yes** **No**	**N %**	11 (55%) 9 (45%)	12 (60%) 8 (40%)	2 (10%) 18 (90%)	**0.002***	0.749	**<0.001***	**0.002***
Smoking **Yes** **No**	**N %**	1 (5.0%) 19(95.0%)	8 (40.0%) 12 (60.0%)	0 20 (100%)	**<0.001***	**0.009***	**0.002***	0.317

***: Significant level at p value< 0.05**

CBC of studied groups **Table (2)** showed statistical significance decrease of Hb, platelets and absolute lymphocyte count among ICU when compared with non ICU and control (p=0.03, 0.003, 0.048 respectively). While, Absolute neutrophilic count was increased (p=0.003). Moreover, the inflammatory parameters included in this study as CRP, ESR and ferritin were statistically significance increase in both ICU and non ICU as compared with control (p=0.0001) **Table (3).**

Table (2): Comparison of different hematological parameters between studied groups:

CBC	Group I		Group II	p value	ICU vs non-ICU	ICU vs control	Non-ICU vs control
	Non-ICU N= 20	ICU N= 20	Control N= 20				
Hb (g/dl) **IQR** **Mean ± SD** **Median**	(10.8 – 15.2) 13.3 ± 3.1 13.3	(9.1 – 13.3) 11.6 ± 2.7 11.3	(12.8 – 15.1) 13.6 ± 1.8 13.5	0.038*	0.101	0.012	0.38
TLC (x 10^3 cell/cmm) **IQR** **Mean ± SD** **Median**	(7.8– 17.9) 13.4 ± 6.6 12.2	(6.9–14.7) 11.4 ± 5.3 11.5	(6.9– 10.3) 8.9 ± 2.3 9.2	0.074	-	-	-
Platelets (x 10^3 /cmm) **IQR** **Mean ± SD** **Median**	(217 – 336.8) 266.0 ± 95.1 251.5	(165.5 – 259.3) 202.0 ± 78.5 197	(192.8-337.5) 267.6 ± 74.3 256	0.048*	0.037*	0.029*	0.921
Absolute lymphocytic count(/mm^3) **IQR** **Mean ± SD** **Median**	(1132.5–1964.3) 1665.7 ± 772.1 1434	(520 – 1432.5) 966.9 ± 587.4 801	(1781–3092.3) 2534.5 ± 1056.8 2560	0.0001*	0.039	0.0001*	0.003*
Absolute neutrophilic count(%) **IQR** **Mean ± SD** **Median**	10978.4 ± 6297.6 9301.5 (5507.3 – 15730.5)	9598.5 ± 4840.6 9663.5 (5172 – 12651.0)	5590.7 ± 1596.3 5602 (4422.0 – 6688.5)	0.005*	0.589	0.01*	0.003*

***: Significant level at p value< 0.05**

Table (3): Comparison of inflammatory parameters among studied groups:

	Group I		Group II	p value	ICU vs non-ICU	ICU vs control	Non-ICU vs control
	Non-ICU N= 20	ICU N= 20	Control N= 20				
CRP (mg/dl)				0.0001*	0.012*	0.0001*	0.0001*
IQR	(6 –21)	(24 – 48)	(1 – 3)				
Mean ± SD	12.9 ± 10.8	38.0 ± 28.4	2.2 ± 1.1				
Median	8	24	2				
ESR (mm/hr) (1st hour)				0.0001*	0.144	0.0001*	0.0001*
IQR	(12.8 – 53.8)	(22.5– 73.8)	(2 – 4)				
Mean ± SD	37.7 ± 33.2	56.0 ± 34.1	3.8 ± 1.6				
Median	22.5	55	4				
S. Ferritin (ng/ml)				0.0001*	>0.99	0.0001*	0.0001*
IQR	(489.3–1150)	(505.8– 972)	(52 –168.8)				
Mean ± SD	742.9 ± 346.2	715.5 ± 336.9	109.3 ± 81.4				
Median	669.3	719	72				

***: Significant level at p value< 0.05**

Regarding to coagulation parameters among studied groups **Table (4)**, there was increase in D.dimer level in ICU and non ICU patients (p<0.001, 0.014) (Figure 1). But, when comparing level of fibrinogen, there was decrease in its level in non-ICU IQR from 0.8- 1.8 g/l when compared with control group (p=0.0001) and then fibrinogen start to increase in ICU patients IQR from 1-4.7 when compared with non ICU patients (p=0.029). Anothor biomarker included in present study was P-selectin **Table (5)**, we demonestrated increase in P -selectin level in ICU patients when compared with non ICU patients and control group (p=0.0001), there was also statistical significance increase when compared non ICU patients with control group (p=0.0001)

Table (4):Comparison of coagulation parameters among studied groups:

	Group I		Group II	p value	ICU vs non-ICU	ICU vs control	Non-ICU vs control
	Non-ICU N= 20	ICU N= 20	Control N= 20				
D-dimer (mcg/ml)				0.002*	0.327	<0.001*	0.014*
IQR	(0.1 – 0.8)	(0.2– 1.7)	(0.1 – 0.2)				
Mean ± SD	0.9 ± 1.9	1.7 ± 3.4	0.2 ± 0.1				
Median	0.3	0.5	0.2				
Fibrinogen (g/l)				0.0001*	0.029*	0.061	0.0001*
IQR	(0.8 –1.8)	(1– 4.7)	(2.4 –3.8)				
Mean ± SD	1.4 ± 1.1	2.7 ± 2.0	2.9 ± 0.8				
Median	1.2	2.1	2.9				

***: Significant level at p value< 0.05**

Table (5): P-selectin level among studied groups:

	Group I		Group II	P Value	ICU vs non-ICU	ICU vs Control	Non-ICU vs Control
	Non-ICU N= 20	ICU N= 20	Control N= 20				
P-selectin (ng/ml) IQR Mean ± SD Median	(45.3–66.8) 67.6 ± 39.9 57	(55 –152.8) 143.4 ± 192.4 64	(26.3 –38.8) 51.3 ± 78.6 31	0.0001*	0.159	0.0001*	0.0001*

***: Significant level at p value< 0.05**

When we made correlations between fibrinogen, P- selectin, D dimer and inflammatory parameters, we found no statistical significance correlations. But, correlations between these special biomarkers and TLC, absolute Lymphocytic count, neutrophilic count and monocyte count, only statistical significance weak positive correlation between soluble p-selectin with absolute monocytic count was recorded (r=0.34, p=0.032) **Figure (1).**

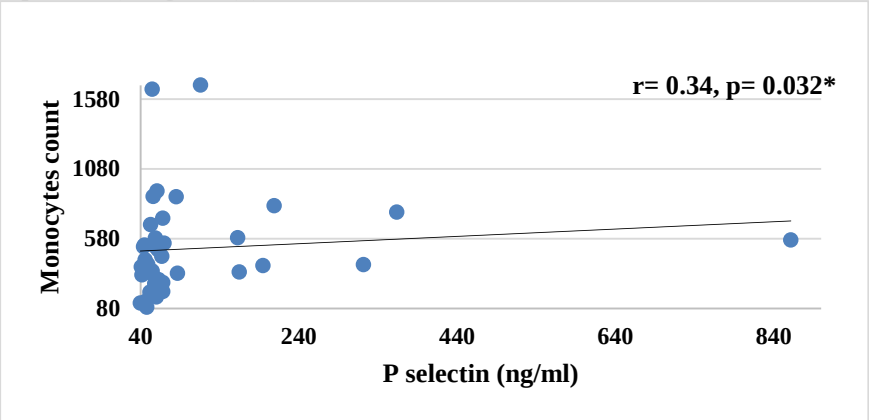

Figure (1): Correlation of Pselectin with monocytic count level in patient groups

The ROC curve study of three biomarkers, revealed that all of them had the same sensitivity 75% while fibrinogen was more specific 97.22% than P-selectin 86.11% and D-dimer 69.44%. The area under the fibrinogen ROC curve AUC was 0.993 and the cut-off value was ≥ 5.255 (p<0.001) **figure (2)**. The area under the P-selectin AUC was 0.917 and the cut-off value was ≥ 101.5 (p= 0.007) **figure (3)**. Finally area under the D-dimer AUC was 0.812 and the cut-off value was ≥ 0.55 (p= 0.042) **figure (4)**.

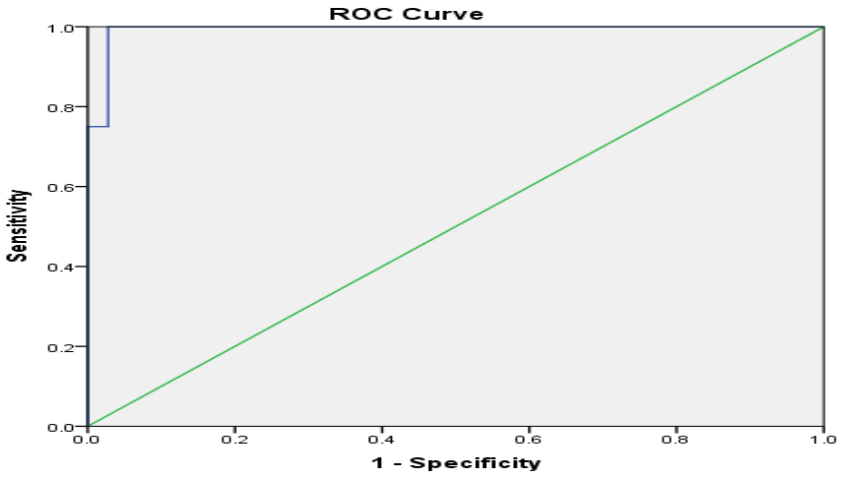

Figure (2): ROC curve of fibrinogen as a prognostic marker for outcome.
AUC (Area under the curve) = 0.993, p value <0.001*, Cut-off point ≥ 5.255 (bad prognosis)

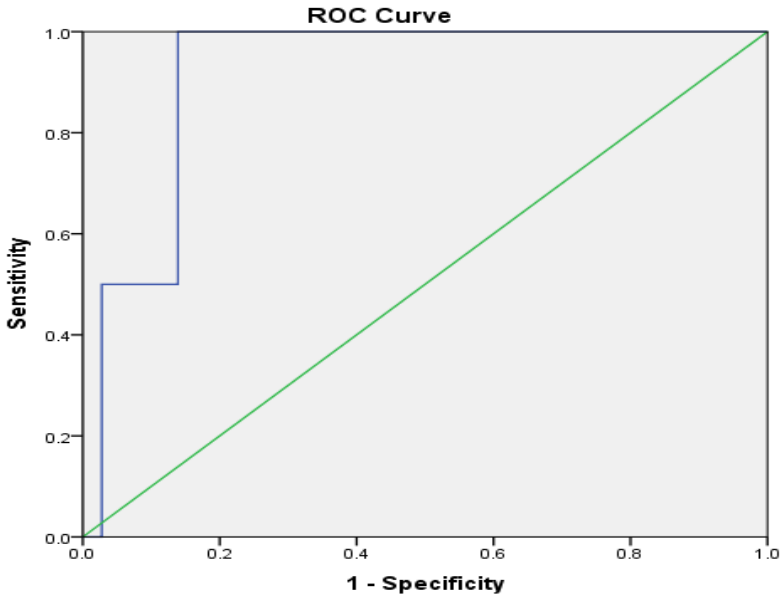

Figure (3): ROC curve of P-selectin as a prognostic marker for outcome.
AUC (Area under the curve) = 0.917, p value = 0.007*, Cut-off point ≥ 101.5 (bad prognosis)

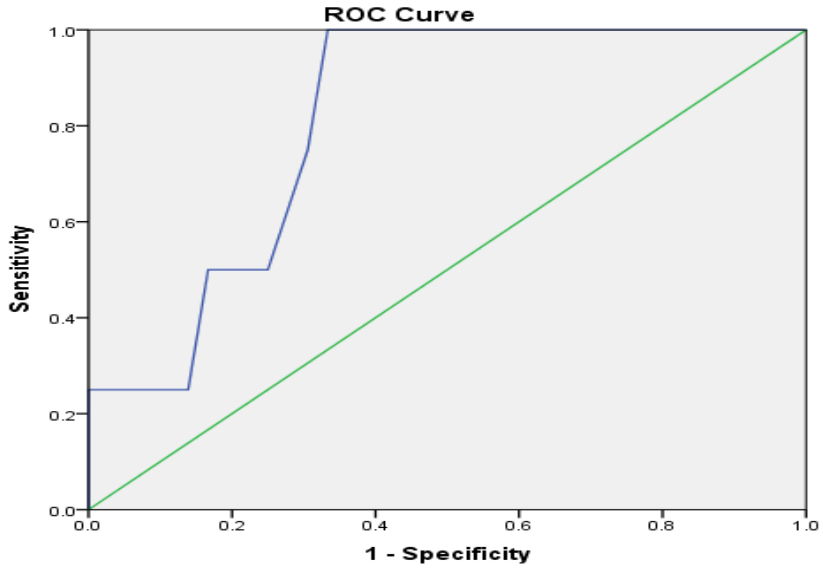

Figure (4): ROC curve of D-dimer as a prognostic marker for outcome.
AUC (Area under the curve) = 0.812, p value = 0.042*, Cut-off point ≥ 0.55 (bad prognosis)

Discussion

COVID-19 became a pandemic situation due to easy transmission of coronavirus[13]. COVID-19 disease manifestations range from asymptomatic cases to severe pneumonia, as well as sepsis, multi-organ failure, and acute respiratory distress syndrome [1]. It is linked to significant morbidity, mortality and can rapidly progress to acute respiratory distress syndrome or venous thromboembolism [14]. According to reports from all around the world, COVID-19 infection has been associated with early laboratory alterations[15]; furthermore, clotting abnormalities which were linked to COVID-19 complications and prognosis [10].There is a growing interest in the role of biomarkers in the screening and early diagnosis of corona virus infection at emergency departments. The goal of our research was to determine the prognostic value of common parameters in predicting the

severe form of COVID-19 which is defined by acute respiratory distress syndrome at the time of hospital admission [8].

In this work, there was increase in age when comparing patient group with control group, and this was in agreement with the research that reported by the US Center for Disease Control and Prevention (CDC) that there was a significantly higher rate of hospitalizations among older adults than any younger age groups [16]. But when comparing age between non-ICU patients and ICU patients in our study, there was no significant difference. Also in our study, there were increase in percentage of comorbidities as diabetes mellitus and hypertension when comparing patient group with control group, and these were in agreement with analysis that found that pre-existing comorbidities were strongly correlated with the increased disease severity[7]. There was no significant difference when comparing percentage of comorbidities between non-ICU patients and ICU patients in our work.

Our study on CBC revealed that there was decrease in the level of haemoglobin when comparing patient group with control group however there was no significant difference when comparing non-ICU patients with ICU patients. This was supported by the study that found COVID-19 patients are anaemic. One of the studies claimed that COVID-19 caused interference in heme synthesis thereby decreasing haemoglobin concentration [17].In this work, there was decrease in platelet count when comparing patient group with control group. Also, we found that platelet count was lower in ICU patients than non-ICU patients which was in agreement with a study found that platelet count was lower in the severe group (ICU patients) than in the non-severe group (non-ICU patients) [18]. The decrease in platelets count is due to direct effect on bone marrow, immune damage and thrombosis [19]. As regarding absolute neutrophilic count in our work, we found that there was increased ANC in patient group when compared with control group, and this was agree with the research that found increase in absolute neutrophilia in covid-19 patients [20].

COVID-19 leads to neutrophil production and lymphocyte apoptosis. Thus, neutrophilia coincides with lymphopenia. Additionally, neutrophilia can be secondary to a superimposed bacterial infection, which is more likely to occur in patients with severe disease [21]. When comparing ANC between non-ICU patients and ICU patients, we found no significant difference in our study. The absolute lymphocytic count, CRP and ESR, our work showed that there were decreased absolute lymphocytic count, increased CRP and increased ESR when comparing patient group with control group, and these were supported by the study of Shang et al., 2020. SARS-CoV-2 may bind directly to lymphocytes and cause lysis. Infection also results in the production and release of inflammatory cytokines which promote lymphocyte apoptosis and lead to atrophy of lymphoid organs, thus decreasing lymphocyte regeneration. CRP is an acute-phase reactant and is a sensitive biomarker in various inflammatory conditions, such as infection and tissue damage [21]. When comparing CRP in two patient subgroups, there was increase in CRP level in ICU patients more than non-ICU patients, and this finding was similar to the study of Shang et al., 2020. But when comparing absolute lymphocytic count and ESR between non-ICU patients and ICU patients, there were no significant difference in this work.

In the present study, there was increase in level of s. ferritin when comparing patient group with control group which was in agreement with analysis that found elevated levels of ferritin in covid-19 patients. Ferritin not only has the role of iron storage but is also a well-known acute phase reactant [22]. But there was no significant difference when comparing s. ferritin between non-ICU patients with ICU patients in our study.

As regarding fibrinogen level in our study, we found that fibrinogen level was decrease in patient group when comparing with control group ($p = 0.0001$), and this was in agreement with the results that found decrease in fibrinogen levels in covid-19 patients [23]. This indicates that measuring fibrinogen can be helpful as prognostic marker in COVID-19 patients admitted to the hospital [24]. And in disagreement with the research that mentioned that the level of fibrinogen is higher in Covid-19 patients compared to healthy controls ($p < 0.001$) [25]. When comparing fibrinogen level in

two patient subgroups, we found that it was increase in ICU patients more than non-ICU patients, and this finding was similar to the research that found that fibrinogen level in patients admitted to ICU are significantly higher than non-ICU patients [26]. Additionally, contrary to the research mentioned that the combined results of fibrinogen levels in studies showed a significant increase in fibrinogen levels in both severe and non-severe COVID-19's patients (p =0.0003**)** [8].

In this work, there was increase in D-dimer level when comparing patient group with control group (p =0.002), and this was in agreement with the observation that found that patients with COVID-19 frequently have significantly increased D-dimer values (p <0.0001) [27]. furthermore, it should be noted that increased D-dimer is a highly non- specific marker of venous thromboembolism (VTE) and may indicate inflammation rather than thrombosis (p <0.0001) [28]. Similar to the study that stated elevated D-dimer levels among hospitalized patients have been related with poor prognosis [10]**.** Our study is further supported by the research that found that D-dimer levels are frequently higher in patients infected with corona virus [29]. And in disagreement with a research where there was no change in D-dimer values in covid-19 patients [30]. When comparing D-dimer level between non-ICU patients and ICU patients in our study, there was no significant difference.

Our results revealed that there was increase in level of sP-Selectin when comparing patient group with control group (p =0.0001) which was in agreement with Venter et al., that reported elevated serum sP-Selectin levels in COVID-19 patients in his study [31]. P-selectin levels were shown to be higher in ICU patients compared to a control group in a study conducted by Goshua et al., (p=0.0014), and it was suggested that sP-Selectin could be a useful biomarker in predicting the severity of COVID-19 infection [32]. And in disagreement with Venter et al., who found that serum sP-Selectin levels were lower in COVID- 19 patients compared to a control group [30]. When comparing sP-selectin level in two patient subgroups in our study, there was no significant difference between non-ICU patients and ICU patients which was similar to the study of Agrati et al., that found serum sP-Selectin level to be high in Both ICU and non ICU covid-19 patients, But there was no significant difference in sP-Selectin levels between ICU and Non-ICU groups [11].

Conclusion

All physicians are extremely concerned about the worldwide emergency and spread of COVID-19 and its wide range of symptoms. Therefore, readily available biomarkers including D-dimer, fibrinogen, and p-selectin are useful for determining and suspecting the fate of COVID-19, particularly in patients who are hospitalised.

Conflict of interest: None.

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